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THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 69 NUMBERS 1 & 2 JANUARY/MARCH 2002

THEME ISSUE

FIFTIETH ANNIVERSARY OF THE DEPARTMENT OF ANESTHESIOLOGY AT THE MOUNT SINAI MEDICAL CENTER

David L. Reich, Ronald A. Kahn, and George Silvay, guest editors

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Introduction

Paul L. Goldiner, M.D., D.D.S.[1], David L. Reich, M.D.[2],
Ronald A. Kahn, M.D.[2], and George Silvay, M.D., Ph.D.[2]

To mark the occasion of the fiftieth anniversary of the founding of the Department of Anesthesiology of The Mount Sinai Hospital, we are pleased to present this issue of *The Mount Sinai Journal of Medicine*. In 1951, when the Department of Anesthesiology was founded, the profession of anesthesiology was in its infancy. The department and the profession have grown together, to the point where they have both made major contributions to the practice of medicine. To celebrate and highlight these contributions, we have gathered articles covering a broad range of topics. Yet they represent only a small portion of the scientific output of our colleagues and alumni.

The Department of Anesthesiology of the Mount Sinai Medical Center has trained many leaders in the field. Many of these physicians have moved on to other institutions and carried on the dissemination of knowledge and clinical excellence. We hope that the future will be even more productive than the past. We would also like to thank the editorial staff of *The Mount Sinai Journal of Medicine* for their help with this project.

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Anesthesiologists and Surgeons at Mount Sinai:

A Partnership in Excellence

ARTHUR H. AUFSES, JR., M.D.

Abstract

Although anesthesia was available to patients when the doors of The Jews Hospital opened in 1855, "professional anesthetists" were not appointed to the staff until 1902. This article traces the history of the anesthesiology staff and department, and documents their accomplishments over the past century.

Key Words: Anesthesiology, history, The Mount Sinai Hospital.

THE SUCCESSFUL DEMONSTRATION of ether anesthesia by Dr. William Morton in 1846 was followed one year later by the introduction of chloroform by Sir James Simpson. These discoveries set the stage for the more complex, sophisticated forms of surgery to be performed in modern hospitals. One of these new facilities was the Jews Hospital, in New York City, which opened its doors in 1855. Although it is not recorded in the casebook, we can assume that the first patient, admitted on June 8, 1855 with a rectal fistula and successfully operated upon by Dr. Israel Moses, was sedated with one of these anesthetic agents. The first recorded use of anesthesia at the new hospital occurred on September 30, 1855, when Dr. Alexander Mott removed "20 enlarged glands of various sizes, requiring more than two hours to complete the operation, the patient being under the influence of chloroform." The operation was performed on a young woman, to remove her tuberculous cervical glands (1).

It would be almost a half-century later before "professional anesthetists" were appointed to the staff of the facility, now known as The Mount Sinai Hospital. Before then, anesthesia was given by either the untrained house staff or other members of the surgical staff. The anesthetic agents were often administered to patients on the wards or in their rooms, shortly before transport to the operating room. Major problems frequently occurred. This led Dr. Samuel Brickner of the Gynecology service to comment in 1895 concerning anesthesia services (2): "It is well for us occasionally to pause in the midst of routine practice to inquire whether the methods that have characterized our work are the correct ones, in view of modern light, and whether we can improve on them to our satisfaction, and to the welfare of those who see fit to put themselves under our professional guidance and care." After speaking about the "sins of omission," such as when a patient about to undergo anesthesia is allowed fluid or food intake and is thereby exposed to the dangers of aspiration, Brickner stressed the need to train young anesthetists and stated: "Make the young men who act as controllers of life and death read some standard work on anesthesia . . . and pass a rigorous examination before a committee of attending surgeons before the lives of patients are entrusted to their willing but helpless care."

Following a death in 1898, the Medical Board decided that "anesthetization in the future shall be carried out by two members of the house staff in place of one unless otherwise ordered by the operator." The Board of Directors (Trustees) continued to be concerned and pressed the Medical Board for further action. After prolonged consideration, they created the position of anesthetist in March 1902, and within a month, two physicians, Drs. M.L. Maduro and C.P. Denton, were appointed. They "went on duty as instructors of anesthetics to the House Staff" and were expected to be on duty for six months each during the year, to instruct incoming House Staff in "the principles and administration of the various general anes-

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thetics" and to be on call "to administer anesthetics to such ward and private patients as the surgeon may desire" (3). By 1903, two anesthetizing rooms and two recovery rooms were built opposite the operating rooms, and the administration of anesthetics in private rooms and wards was eliminated.

In their first report (3), the two anesthetists strongly recommended the use of nitrous oxide and ether, rather than ether alone, on the basis of safety. Because of Maduro and Denton's preferences, the use of chloroform declined, but when it was used, caffeine was first given by injection. It was believed that caffeine was a respiratory stimulant and that it had a good effect on the heart, preventing the initial fall in blood pressure which could occur with induction of anesthesia with chloroform (3). Maduro had published a number of articles, including a description of an adaptation of an earlier anesthetic apparatus of Hewitt, a British anesthesiologist, which allowed for continuous administration of chloroform during head and neck, and throat procedures (4, 5).

Drs. Maduro and Denton quickly gained credibility within the institution for their service as well as their research. Their investigation into the causes of postoperative pneumonia found that body cooling during or after surgery, and unclean rubber breathing bags in the anesthesia apparatus, were important factors in the development of this complication. They recommended maintaining body heat with blankets and boiling the rubber bags for five minutes (3).

In 1905 Dr. Thomas Bennett was appointed to the staff. Already well known for developing the Bennett apparatus for the administration of nitrous oxide and ether, he would remain on the staff until his death in 1932. Bennett, originally from Kansas, was on the staff of both the Roosevelt Hospital and the Hospital for the Relief of the Ruptured and Crippled (today known as the Hospital for Special Surgery), and would eventually be placed in charge of anesthesia at the Presbyterian Hospital (6). He had published significant articles prior to joining our staff (7–9).

In 1884, Dr. Carl Koller in Vienna introduced cocaine for clinical use as a local anesthetic (10). It has been stated (11), "The reading of [Koller's] first paper on the subject at an ophthalmological congress in Heidelberg marks the inception of the modern period in anesthetic practice." After Koller joined the staff in 1890, cocaine became a very popular local anesthetic at Mount Sinai. He served for many years as chief of Ophthalmology. In 1903 Maduro noted that "local anesthesia in the general surgical service has been made use of in such operations as herniotomies, colostomies, and gastrostomies. A number of such operations begun by this method have been finished under general anesthesia" (3).

Spinal anesthesia did not fare as well at Mount Sinai. It was first performed successfully in humans by August Bier in Kiel, Germany, in 1898. Maduro commented four years later (3): "We are happy to say that subarachnoid cocainization has been performed but once within the past two years. The dangers attendant on the use of this method have influenced our surgeons to consider it as still in the experimental stage of development."

Dr. William Branower, a graduate of the Columbia University College of Physicians and Surgeons (1904) who had served his internship and surgical residency in the private pavilion at Mount Sinai, was appointed as anesthetist in 1908 "at a salary of $100.00 for the six months." At the same time he served as a surgeon in the outpatient department. Named a "supervising" anesthetist in 1923, Dr. Branower and Bernard Eliasberg served as the nominal heads of the anesthesia service for 20 years until Branower's retirement. In 1936, Branower developed a respirator which was widely accepted and used for many years (12).

An important event in the history of anesthesia occurred at Mount Sinai on February 20, 1910 (11). On that date, Dr. Charles Elsberg, who had completed his training in 1895 and thereafter served as a member of the Surgical Service, administered the first intratracheal insufflation of anesthesia in humans. It was based upon the experimental work of Meltzer and Auer of the Rockefeller Institute. Using a portable anesthesia apparatus designed with the help of Dr. Bernard Eliasberg, Elsberg, after extensive animal studies (13), tested the technique by successfully administering oxygen to a comatose patient with advanced myasthenia gravis. Although that patient died, the technique proved feasible. Shortly thereafter, Elsberg successfully administered anesthesia for the drainage of a lung abscess by thoracotomy performed by Dr. Howard Lilienthal. This success was followed by a procedure on a patient who had drainage of an empyema. Elsberg presented the work before the New York Surgical Society on May 11, 1910. Subsequently published in the *Annals of Surgery*, the last sentence of the paper presages the development of thoracic surgery (14): "If the future will show that it is as safe for the human being as it is for the animal — and our experiences seem to point in that direction — then surgery will have a very simple method for the prevention of the dangers from acute pneumothorax, a danger which has been the chief hindrance to the development of intrathoracic thoracic surgery." Lilienthal, in reporting the surgical aspects of the case, commented (15): "The most notable feature of the anaesthesia . . . was the total disappearance of the rattling respiration which existed during the administration of the ether by the usual method." In a series of papers over the next two years, Elsberg would report on almost 500 cases of intratracheal anesthesia administered for general and thoracic surgical procedures; Eliasberg administered the anesthetic for most of the cases (16–18). A man of many talents and trained in general surgery and neurosurgery, Elsberg would go on to even greater fame in the field of neurosurgery.

In 1910, Dr. Bernard Eliasberg, a graduate of Cornell Medical School who had trained at Mount Sinai, was appointed as the resident anesthetist to the private pavilion. He and Branower, working together, gradually expanded the corps of trained anesthetists, so that by 1940 the staff consisted of more than 10 physician and nurse anesthetists. In 1943, after the death of Branower, Eliasberg was appointed Anesthetist to the Hospital, a position he held until 1950. The service was represented for the first time on the Medical Board. A founder of the New York State Society of Anesthesiologists and an original member of the American Board of Anesthesiology, Eliasberg was also responsible for training the first resident in anesthesiology at Mount Sinai, Dr. Gerda J. Weil, who graduated from the program in 1943. Two years later, Dr. Irma Back served in the program and was joined in 1946 by a second resident.

A gentleman of great knowledge, wisdom and humor, Eliasberg was a superb teacher of a generation of anesthesiologists, and beloved by many. He played a pivotal role in the development of anesthesiology at Mount Sinai. For his service to Mount Sinai and to anesthesiology, Bernard Eliasberg was the first and, to date, the only anesthesiologist to receive Mount Sinai's coveted Jacobi Medallion. Following Dr. Eliasberg's death in 1962, through the generosity of his family, the department, and industry, the Bernard Eliasberg Memorial Symposium was established, an event which continues to the present.

Dr. Milton Adelman was named director of Anesthesia and Anesthesiologist to the Hospital in 1950 upon the retirement of Eliasberg. Appointed to the staff in 1942, Adelman was called to military service in World War II almost immediately thereafter and served with distinction as a regional consultant in anesthesia to the European Theater of Operations. Adelman authored one of the earliest papers on the potential fatal interaction of epinephrine when given during cyclopropane-ether anesthesia, some of the early papers on allergic reactions during anesthesia (19), and on the use of promethazine (20, 21). Adelman developed an automatic controlled respirator which, by relieving the anesthesiologist of the burden of manually inflating the lungs, proved of inestimable value in the management of endotracheal anesthesia (22, 23). The technique also greatly simplified anesthesia in the experimental laboratories, by allowing for continuous endotracheal anesthesia without the presence of an anesthesiologist (24).

Adelman formalized the residency training program, which had five positions in 1950. As the program grew, he gradually phased out the nurse anesthetists who had been on staff. A second year was added to the residency in 1951. In that year the anesthesiology and physics departments developed an electro-shock machine for the treatment of ventricular fibrillation. In 1957, the Inhalation Therapy Department became part of the Anesthesiology Department. Many of the graduates of the program would remain on staff, as the department expanded to keep up with the increasing volume of the surgical services. Joseph Jagust became one of Mount Sinai's premier anesthesiologists. Following Dr. Jagust's early retirement due to illness, the Joseph A. Jagust Award in Anesthesiology was endowed; it is presented annually to a graduating medical student who has excelled in the anesthesiology clerkship.

A most valued colleague of Adelman, Dr. Morris Bien, appointed to the staff in 1943, served Mount Sinai for more than 30 years. A pioneer in the development of techniques for regional anesthesia, Bien was also at the forefront of chronic pain management. He recognized the need for preoperative medication to allay patient apprehension (25), and the need for the anesthesiologist to visit the patient preoperatively, once again to allay fear (26). He symbolized the partnership which existed in Mount Sinai operating rooms between the surgeons and anesthesiologists. In 1946 he stated, "The anesthesiologist has two responsibilities — to the patient and to the surgeon. While he is selecting the best anesthetic agent and the procedure best suited to the patient, he must always bear in mind that the anesthetic risk can be equal to, or less than, the surgical risk; but it can never be greater. The anesthetist makes the surgeon as comfortable as possible, gives him a clear field in which to work, and enables him to devote his entire attention to the operation" (25). Bien also had the distinction of being the first faculty member of the Mount Sinai School of Medicine to have a family member in the school. His son Ralph, now a psychiatrist, graduated with the Class of 1973.

Herman Turndorf, recruited to the staff from Harvard in 1963, left after 7 years to assume the chair of Anesthesiology at West Virginia University School of Medicine. He returned to New York in 1974 to become chair of the Department of Anesthesiology at New York University School of Medicine, a position he held for more than 25 years.

Following the trend to appointment of full-time chiefs of service, Dr. Leslie Rendell-Baker was named chairman of the department in 1962, a position he held for 17 years. Trained in England, Rendell-Baker came to Mount Sinai from Cleveland, where he had been on the faculty at Case-Western Reserve. He was instrumental in setting standards for anesthesia equipment and for the safety of the operating room (27 – 45). Rendell-Baker chaired the International Standards Committee of the American Society of Anesthesiologists for many years. He also played a major role in the development of special equipment for the pediatric population.

The years of Rendell-Baker's tenure, spanning as they did the opening of the medical school, saw enormous growth in the role of the anesthesiologist within the institution. In a major collaborative effort with the Department of Surgery in the late 1960s, Dr. Rendell-Baker and Dr. Allan Kark, chairman of the Department of Surgery, proposed the development of a surgical intensive care unit (SICU) to be operated conjointly and staffed with full-time faculty who would be engaged in patient care, teaching and research. A 5-bed unit already existed, but in this small unit, surgeons were responsible for the care of their own patients. Considerable resistance to the new unit was encountered from both the surgeons, who felt they would lose control of their patients, and the administration, who did not want to absorb the cost of the unit and the salaries of the faculty. The plans were eventually embraced, and the unit opened in 1970, with Dr. William Shoemaker of Surgery as the director and Dr. Christopher Bryan-Brown of Anesthesiology as co-director.

Over the years, the ICU would become a jewel in the crown of Mount Sinai. A complete history of the SICU can be found in the article by Dr. Andrew Leibowitz in this issue of *The Journal* (46).

With the recruitment of Drs. Robert Litwak and Howard Gadboys in 1962, to develop the Division of Cardiothoracic Surgery within the Department of Surgery, a major cardiac surgery program was begun, necessitating the development of a division of cardiac anesthesia. Dr. Barbara Lipton was recruited to head the division, and with her colleagues she made major contributions to the management of these patients (47, 48), especially in the area of the neurological sequelae of open heart surgery (49). Dr. George Silvay, originally recruited by Dr. Litwak as the associate director of the cardiothoracic surgery research group, joined the Anesthesia faculty after completion of his residency. His writings included a number of significant papers on the use of microfilters (50, 51) and on early endotracheal extubation following open heart surgery (52).

Lipton also became the senior anesthesiologist working in the hyperbaric chamber when it was completed. In conjunction with her colleague Dr. Avram Weinreich and with Dr. Julius Jacobson of the Department of Surgery, she conducted a series of elegant experiments on the physiology and role of hyperbaric oxygen (53 – 56). Lipton's career was tragically cut short by her untimely death from breast cancer in 1974 at the age of 46. A letter written by her to the graduating residents just three weeks before her death epitomizes the compassion and humanistic view of the specialty of anesthesiology that has characterized this department throughout its existence. In it she states (57) ". . . the patient must always be uppermost in your thoughts, his welfare the most important thing for you to care about; you must be patient with him and gentle; his anesthetic and surgical procedure may be routine to you, but to him he is experiencing one of the most vital and traumatic days of his life. As an anesthesiologist practicing your profession with skill, you, as a matter of course, will deprive him of his consciousness, respiration, autonomic reflexes. You take him into the great unknown and you are as responsible as any one person can ever be for anyone else, including a parent for a child."

Other significant contributions in the field of anesthesiology were made in many areas during this period. In the rapidly growing Obstetrical Division of Anesthesiology, Roberts' and Shirley's work on the prevention of aspiration pneumonitis during cesarean section was classic (58). A very large institutional program in myasthenia gravis with an emphasis on transcervical thymectomy led to major papers on the anesthetic management of this difficult group of patients. Girnar and Weinreich (59), in a large series of cases, demonstrated for the first time that tracheostomy was not needed for the vast majority of these patients. This was confirmed by others in the department subsequently (60–64). With the recruitment of Dr. Alexander Goldblat, the first professor of anesthesiology in Belgium and a founding member of the World Federation of the Societies of Anesthesiology, the department became heavily invested in the developing area of neuroleptanalgesia.

Caseloads increased consistently. In 1977, the department cared for 18,000 patients, including 3,000 obstetrical patients. The Gaisman Surgical Pavilion, dedicated in 1974, provided 19 new operating rooms and recovery facilities for general and specialty surgery in the newly opened Annenberg Building. It was the first time that a 24-hour-a-day recovery room was available at Mount Sinai.

With the growth of the medical school, the teaching program of the department evolved to include a fourth-year elective for medical students. The residency expanded and a third-year program in cardiothoracic and neurosurgical anesthesia was introduced. In 1962, the Bernard H. Eliasberg Library was created in the department, and the next year the Eliasberg Memorial Lecture was established. The first lecture, "Quantitation in Anesthesia," was presented by Professor William W. Mushin, who, in 1953, had coauthored a major text, *The Principles of Thoracic Anesthesia: Past and Present*, with Rendell-Baker (65). The Memorial Lecture grew to be a full-day symposium in 1971.

Dr. Rendell-Baker retired in 1979 and was succeeded by Dr. David C.C. Stark, the assistant director of the department since 1970. At the time of the transition, there were 44 residents in the department. Dr. Stark, a superb clinical anesthesiologist, also emphasized the importance of research by members of the department. A cell culture laboratory was developed. The three editions of Stark and Roberts' book *Practical Points in Anesthesiology* (1974, 1979, 1985) were all well received (66).

Anesthetic management of the older patient has been an interest of the department for many years (67, 68). More recently, studies of cognitive function during the perioperative period have been studied, both clinically and in the laboratory (69–71).

The appointment of Dr. Joel Kaplan as chairman in 1983 brought to Mount Sinai an internationally known clinician and researcher in cardiac and thoracic anesthesia. Recruited from Emory University School of Medicine, where he had been chief of Cardiothoracic Anesthesia, Kaplan quickly converted the members of the department into a totally full-time faculty. A prolific writer, Kaplan had edited *Cardiac Anesthesia* (72), the primary textbook in the field, now in its fourth edition, and authored major papers on nitroglycerin infusion during coronary artery surgery (73); the precordial electrographic lead in patients with coronary artery disease (74); the optimal management of patients with ischemic heart disease who are undergoing noncardiac surgery (75); and the early diagnosis of myocardial ischemia using the pulmonary artery catheter (76).

In 1986, Dr. Kaplan was named to the then newly created Horace W. Goldsmith Chair in Anesthesiology. In that same year he became the founding editor-in-chief of the *Journal of Cardiothoracic Anesthesia*, the only journal in the field. Kaplan published another seminal paper in 1988, on the role of ultrashort-acting beta blockers in the perioperative period (77).

One of Kaplan's earliest priorities was to create a mandatory anesthesia clerkship for all third-year students in the medical school. This rapidly became most popular and increased the number of our students choosing a career in the specialty.

In 1987, Dr. Randall Griepp was appointed chief of the Division of Cardiothoracic Surgery. He and his team significantly increased the number of cases in the specialty, and the Cardiothoracic Anesthesiology Division also became more active, both clinically and in the research arena. Konstadt and Reich, the co-directors of Cardiac Anesthesia, and their colleagues championed the intraoperative use of transesophageal echocardiography (TEE) and were the first to validate left ventricular function with this modality (78). They helped establish the guidelines for the use of TEE (79), and established its usefulness in detecting atherosclerosis of the ascending aorta during cardiac surgery (80), as well as detecting a patent foramen ovale (81). TEE became a sensitive indicator for the detection of cardiac preload changes induced by transfusion and phlebotomy in the pediatric population (82), as well as helping to determine the severity of mitral regurgitation in the operating room (83). An algorithm was developed to assess intraoperative mean arterial pressure lability (84), and predictors of failure of pulse oximetry data were identified (85).

A Division of Thoracic Anesthesia was also created, and under the leadership of Dr. Edmond Cohen, it produced a number of important papers relating to one-lung ventilation (86–88). Cohen's text *The Practice of Thoracic Anesthesia* (89) has become one of the leading texts in the field.

The 1980s saw the rise of ambulatory surgery and the need to develop, test and provide anesthetics for short-term procedures that would allow the patient to return home the same day in a stable condition (90–94). Computers and automation began to play an increasing role in the department's service. Databases of anesthetics and outcomes were created and work was begun on creating expert systems in anesthesiology.

The institution of the liver transplant program in 1988 provided yet another opportunity for important contributions to the literature in this area from the Division of Transplant Anesthesia. Collaborating with the transplant surgeons, Dr. George Gabrielson and his colleagues showed that flushing a donor liver with autologous blood improved intraoperative hemodynamic stability and early graft function (95). Gabrielson was also the senior author of a major paper on the use of continuous infusion of phentolamine and esmolol in the management of patients with pheochromocytoma (96). This technique has been adopted by almost all centers managing these patients.

As noted earlier, Morris Bien was the first of the anesthesiologists at Mount Sinai to be involved in pain management; at that time, pain management consisted primarily of regional blocks for either acute or chronic conditions. Many years later, Owitz and Koppolu recognized the value of sympathetic blockade as a diagnostic and therapeutic modality and began to employ nerve blocks in the relief of cancer pain (97–99). A formal pain service was organized in the mid-1980s with both inpatient and outpatient components. Postoperative pain therapy with intravenous patient-controlled analgesia (PCA) was begun in 1988. Shortly thereafter, continuous epidural fentanyl infusion was added as a therapeutic option. Both techniques gained rapid patient and surgeon acceptance.

Under the leadership of Dr. Joel Kreitzer since 1991, growth of the pain management service has been exponential. In 1994, a fellowship training program was approved by the Accreditation Council for Graduate Medical Education (ACGME); it now trains four fellows per year. Between 1996 and 1999, patient census doubled, and almost 4,000 procedures were performed on the entire population in 1999. In 1999, almost 5,000 postoperative patients were treated with either IV or epidural PCA. A recently instituted program uses continuous axillary and interscalene catheters for postoperative pain in upper extremity surgery. Concurrently, the case load of the chronic pain service has grown dramatically. Multiple publications dealing with postoperative and chronic pain management have been published, relating to new drugs, new delivery systems, and improved techniques of management (100–111).

The new Guggenheim Pavilion was completed in 1992, and included a 22-room surgical suite, a large recovery area (now called the Post-Anesthesia Care Unit) and 66 specialized intensive care unit beds.

In 1994, Dr. Kaplan encouraged the acquisition of the first computerized, simulated patient in this geographical area. The department has since acquired two more. These mannequin simulators provide a realistic environment for students and residents to practice the administration of anesthetic agents and injected drugs, as well as to measure cardiac output and practice intubation. The program represents Mount Sinai Medical Center's commitment to advancing education and patient safety.

The clinical service flourished under the leadership of Drs. Raymond Miller and Ian Sampson. Superb teachers and mentors of residents, students, and junior faculty, they assumed responsibility for the ever-increasing patient load and the ever-increasing complexity of the cases operated upon. In 1999, 35,000 anesthetics were administered by a faculty of 75 at Mount Sinai. There were, in addition, 36 attending anesthesiologists at Elmhurst Hospital Center, The Bronx VA, Mount Sinai of Queens, and Queens Hospital Center. In the 1999–2000 academic year there were 42 residents and 12 fellows in training.

Dr. Paul Goldiner was recruited to the faculty in 1992. A former chairman of the departments of anesthesiology at Memorial Sloan

Kettering Cancer Center and Albert Einstein College of Medicine, Goldiner had served as president of the New York State Society of Anesthesiology and was widely known and respected for his abilities as a leader and teacher. When Kaplan left the Mount Sinai School of Medicine in 1997 to become dean of the University of Louisville School of Medicine and provost and vice president for health affairs of the University, Goldiner became the interim chair and succeeded to the chairmanship in 1999. When Dr. Goldiner was installed as the second Horace W. Goldsmith Professor of Anesthesiology at the School of Medicine's convocation in 2000, Dean Arthur Rubenstein stated: "You have made seminal contributions to anesthesia and critical care medicine, emphasizing the improvement of perioperative care of cancer patients; initiatives which you have spearheaded in your department at Mount Sinai, such as the expansion of clinical trials, have produced enormous benefits. Under your direction the residency training program in Anesthesia has become one of the leading programs in the country. For your leadership in all three components of the tripartite mission of academic medicine — research, education and patient care — I am delighted to invest you as the second Horace W. Goldsmith Professor of Anesthesiology." With these words, Dr. Goldiner took the helm of an outstanding department.

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The Mount Sinai Hospital's Role in the Development of Anesthesia Safety Standards

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Abstract

The Department of Anesthesiology of The Mount Sinai Hospital was closely involved in introducing anesthesia safety standards for anesthesia breathing systems, the introduction of the first disposable plastic anesthesia breathing system, the layout of the controls on gas machines, nontoxic airways, safe ethylene oxide sterilization and safe obstetrical anesthesia.

Key Words: Safety standards, anesthesia.

Standardization of Anesthetic Equipment

CHAOS WAS THE ONLY WAY to describe the anesthesia equipment situation confronting Colonel Ralph Tovell in the US Army hospitals in Great Britain when he arrived to take charge in 1942 (1). The hospitals were equipped with four different models of gas machines: two British models that only accepted British cylinders and two American models that only accepted American cylinders. The local gas suppliers had to use adapters to fill the US cylinders. Since British carbon dioxide cylinders and US oxygen cylinders were both painted green, errors, some of which resulted in death, inevitably occurred when US oxygen cylinders were filled with carbon dioxide. To further complicate this situation, none of these machines accepted the same sizes of breathing tubes, face masks, ventilation bags or tracheal tube connectors. This incompatibility resulted in nurses and corpsmen bringing parts that would not fit when a sudden need for accessory equipment arose (2).

To ensure a steady market for their expendable rubber components, each US manufacturer of anesthesia apparatus used a different size and design for their face masks and other breathing system fittings. When Weiss' Universal Mask Adapter appeared in 1949, it was greeted as a great boon, because it allowed the use of 8 combinations of 3 sizes of anesthesia inhaler castings with 5 types of face masks (3) (Fig. 1).

To address these issues of equipment incompatibility, the American Society of Anesthetists (ASA) — now known as the American Society of Anesthesiologists — formed a Committee on Standardization. In 1942, Colonel Tovell recommended to the Surgeon General that efforts to standardize threads, tapers, outlet sizes, valves and interchangeability of rubber parts (such as masks, breathing and endotracheal tubes) be supported. Unfortunately Tovell's advice was not followed, and there was no progress until 1956. At that time, Ralph Tovell, now of Hartford, Connecticut, Vincent Collins of New York, other members of the

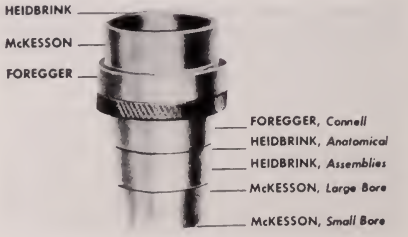

Fig. 1. Weiss's Universal Mask Adapter (1949). Reproduced with permission (3).

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Dr. Rendell-Baker served from 1962 – 1968 as chairman and from 1968 – 1979 as vice chairman of the Z79 Anesthesia Standards Committee of the American National Standards Association. From 1972 – 1976 he was chairman of the FDA Anesthetic Devices Classification Panel, and from 1975 – 1979 he was a member of the Board of Directors of the American National Standards Institute

ASA Committee on Standardization, and manufacturers formed the American National Standards Association's Sectional Committee Z79, with Hamilton S. Davis of Cleveland as chairman (1). The first items considered were standards for tracheal tubes and tracheal tube connectors. They decided against continued use of Magill's arbitrary tracheal tube sizes of 00 to 10 and the French catheter gauge sizes (which indicated the external circumference of the tracheal tube). Rather, the internal diameter of the tracheal tube, measured in millimeters, was chosen since this indicated the sizes of the airway provided and a connector appropriate for a given tracheal tube. The 15-mm conical fitting was adopted, because it permitted a better airway than the 11-mm size.

In 1958, the US committee became aware that the British Standards Committee, SGC 15, had adapted a draft standard for anesthesia breathing systems using metal 23-mm diameter male and female conical fittings joining rubber components throughout the system. At the first joint US/UK meeting, held in London in July 1958, the British suggested that the American committee adopt this as the basis for a US/UK standard.

At the 2nd joint US/UK meeting, in New York in December 1958, two US and one UK sizes of fittings were considered. After several days of discussion, a 22-mm fitting was adopted, and it was agreed that all face masks, including the pediatric sizes, would have 22-mm female orifices. That would permit anesthesia to be given in an emergency using a pediatric mask with an adult breathing system. To connect this new 22-mm pediatric mask orifice to the 15-mm fittings that were used throughout the rest of the pediatric breathing system, a new adapter was designed which had a 22-mm male fitting with an internal 15-mm female fitting. This was found to be so useful that it was included in all the breathing systems (Fig. 2).

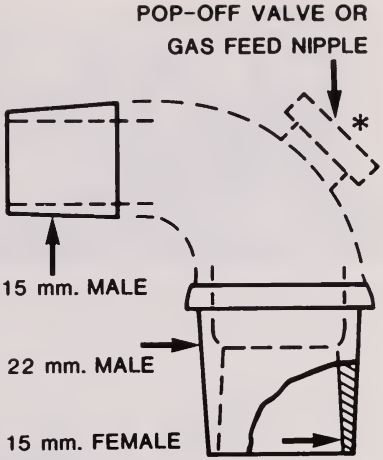

Fig. 2. Pediatric mask-tube adapter introduced in the 1961 draft of the pediatric breathing system standard to bridge the gap between the newly introduced pediatric masks with their adult 22-mm orifices and the 15-mm fittings in the rest of the pediatric breathing systems. A version without the pop-off valve or gas feed nipple soon became an indispensable part of adult systems.

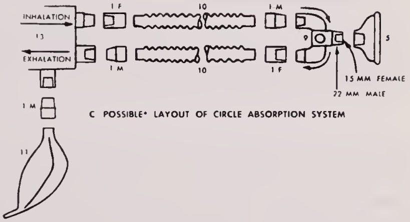

Fig. 3. Proposed adult breathing system with male-female fittings in "gas flow sequence" (1965).

At that time Y-pieces with valves were popular, but they could cause accidents if two sets of valves, one on the absorber and the other in the Y-piece, were inadvertently in opposition. It would then be impossible for the patient to inspire or for the anesthesiologist to deliver positive pressure to the patient's lungs. To avoid this hazard, 22-mm conical fittings in a male-female sequence in the direction of gas flow were specified in the proposed standard breathing system (Fig. 3). Unfortunately when these breathing systems were field tested, the British-made hard rubber female fittings (Figs. 4 and 5) that were used by many of the US manufacturers became distorted when heat sterilized, and the systems fell apart (4). The gas flow sequence was rejected, and further work on that standard was deferred.

In 1962 Hamilton S. Davis was appointed chairman of the new Department of Anesthesiology at University of California, Davis and resigned from the committee. The author, having been recently appointed director of the Department of Anesthesiology at The Mount Sinai Hospital in New York, took over the chairman-

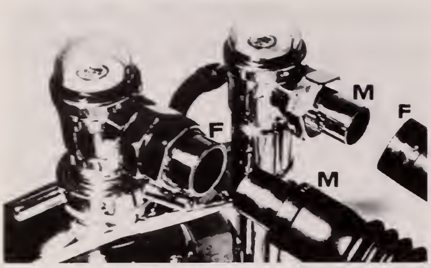

Fig. 4. (M) male and (F) female metal fittings on the absorber and hard rubber (M) male and (F) female fittings on the corrugated tubings (© L. Rendell-Baker, 1967).

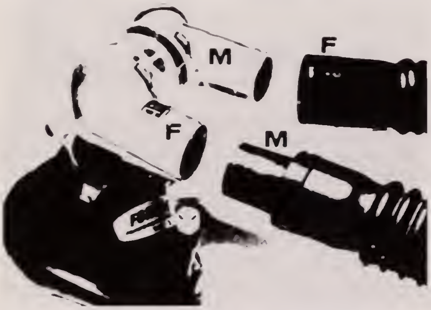

Fig 5. Metal (M) male and (F) female fittings on the valved Y-piece and hard rubber fittings on the tubing. These rubber female fittings distorted when heated during sterilization (© L. Rendell-Baker, 1967).

ship. For convenience, many of the Z79 committee meetings were held in the "rumpus room" lounge of The Mount Sinai Hospital Nurse's Home. The attendance sheets from these meetings indicate the sandwich each individual ordered for lunch from the nearby K & D Deli. That enabled the meetings to proceed without interruption. From that point onward, The Mount Sinai Hospital became closely associated with nationwide efforts to enhance the safety of anesthesia and medical equipment.

It was not until 20 years later that the metal inserts in the rubber components were eliminated from the anesthesia breathing system, resulting in a simple system almost identical to that proposed by the British in 1958. This was adopted as the international standard for breathing systems (Fig. 6). Robert Bryan Roberts, the director of Obstetrical Anesthesia at The Mount Sinai Hospital, New York (Fig. 7) and the chairman of the Z79 Ethylene Oxide Subcommittee, was interested in the problems of cross infection (5) and the difficulty associated with the sterilization of the existing heavy rubber and metal breathing systems. The recently established standardized anesthetic circuits were noted by Thomas J. Mahon, a New Jersey busi-

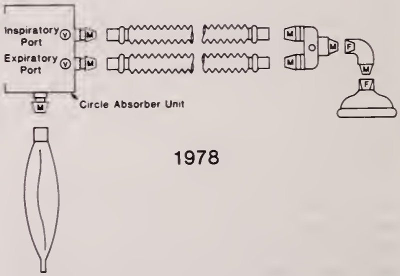

Fig. 6. International standard for adult circle breathing adopted in 1978.

Fig. 7. Robert Bryan Roberts, M.D. (1933–1983) 1974 photograph (©L. Rendell-Baker, 1974).

nessman, who imported new equipment capable of fabricating light-weight, corrugated plastic tubing that he felt might be useful as disposable respiratory therapy breathing systems. Roberts persuaded Mahon to focus his attention on the development of a disposable anesthesia breathing system for which Roberts designed a plastic swivel connector that was permanently bonded to the breathing tubes (Fig. 8). This first disposable anesthesia breathing system was introduced at the ASA Convention in Washington in October 1968 (5).

Aspiration Pneumonitis Prophylaxis

In 1974, Roberts and Michael Shirley of The Mount Sinai Hospital's Division of Obstetrical Anesthesia carried out an extensive review of the hazard of acid aspiration during anesthesia for cesarean section (6). Their studies indicated that this hazard could be minimized by administration of oral antacids. As a result of this study, they introduced a routine in which all patients received a dose of liquid antacid by mouth every three hours during labor or as soon as the decision to perform a cesarean section was made.

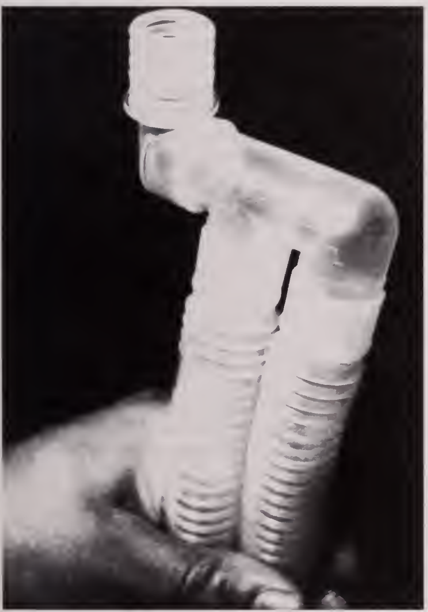

Fig. 8. Disposable anesthesia system and swivel Y designed by Robert Bryan Roberts and Thomas J. Mahon in 1968 (©L. Rendell Baker, 1974).

In addition to this pharmacological prophylaxis, changes in anesthetic techniques were instituted to reduce the incidence of aspiration. Intermittent positive pressure ventilation via mask in an anesthetized patient may result in gastric insufflation of air. The resultant increases in intragastric pressure may result in a greater risk of regurgitation with subsequent aspiration. In order to avoid the need for positive pressure ventilation via mask, patients breathed 100% O_2 before induction of anesthesia to increase the alveolar oxygen concentration. This allowed a somewhat longer interval for patients to safely remain apneic without developing arterial oxygen desaturation after induction of anesthesia and prior to endotracheal intubation with a cuffed endotracheal tube. This simple routine was vigorously advocated and soon became generally accepted.

Thermoregulation

In 1976, Henry Tausk, Raymond Miller, and Roberts of The Mount Sinai Hospital Department of Anesthesiology described the use of a prototype apparatus to warm and humidify the inhaled anesthetic gases to maintain body temperature during anesthesia associated with prolonged neurosurgical operations (7). Their work was greatly expanded by Jack Chalon and Herman Turndorf, former members of the department, who published the definitive work on the subject in 1981 (8). Though servo-controlled humidifiers and convective air warming devices became available later, they were less convenient than the widely used compact combined heat and moisture exchangers that also functioned as bacterial filters.

Toxic Substance Control

In 1967 Symchych and Cadotte (9) described tracheal necrosis following prolonged intubation and ventilation in infants. Later investigation by Guess and Stetson provided evidence that the toxic organo-tin stabilizers used in the manufacture of the PVC tracheal tubes were responsible (10). Since the use of this compound appeared to be widespread, it was clear that the forthcoming publication of their report in the absence of safe alternatives would cause a crisis. In December 1967, the chairman of Committee Z79 called an emergency meeting, to be held in New York, of all US, British, German and French manufacturers supplying the US market to review this report by Guess and Stetson. The manufacturers agreed that the PVC tracheal tubes containing the toxic stabilizers would be withdrawn from the US market. They would be replaced by tracheal tubes that would satisfy the US Pharmacopoeia's Rabbit Muscle Implantation Test. This test, designed to demonstrate that a material would not induce any evidence of tissue toxicity, was already required by the US Army. These new tracheal tubes, marked "Z79 I.T.," were to be tested in this manner and were to be available three months later when Guess and Stetson's report was scheduled to be published. A notice was mailed to all members of the ASA advising them to check the safety of the tracheal tubes used in their hospitals with their suppliers. Since that time, all equipment coming into contact with the patient's tissues must satisfy a similar test.

Another problem that came to light during this investigation was that many hospitals using ethylene oxide sterilization were not allowing adequate time for elimination of the gas from rubber and PVC items after sterilization (4, 5). A Z79 Ethylene Oxide Subcommittee, formed with Roberts as chairman, argued for the need for heated aerators. For the first time, in their Guide to Hospital Personnel on Ethylene Oxide Sterilization, the aeration conditions necessary to remove these gas residues were described. According to American National Standards rules, Z79's scope was limited to standards for anesthesia and ventilatory equipment. This subcommittee was therefore transferred to the Association for Advancement of Medical Instrumentation's Committee on Sterilization. Their work became a national resource on sterilization problems, and they issued guidelines on gas, steam, and radiation sterilization, which were cited by the Food and Drug Administration (FDA), Occupational Safety and Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH). OSHA eventually reduced the 8-hour time-weighted average exposure to ethylene oxide in the workplace from 50 parts per million (ppm) to 1 ppm. To meet this level, ethylene oxide gas mixtures were used in closed recycling systems in sterilizers, which repeatedly purged their chambers at the end of the sterilization cycle to eliminate spillage of the gas into the workplace, allowing the gas mixture to be retrieved and reused.

Anesthesia Machine Standardization

Until 1979 there was no uniformity in the design and layout of the controls on anesthesia gas machines, and this lack of uniformity often led to accidents. In that year, the Z79 Committee completed work on standard Z79.8, which established standards for the performance and safety of anesthesia gas machines. These guidelines required that all controls and gauges be clearly visible to an operator seated or standing 1 meter in front of the machine at a specified light level. The marking and calibrations were to be simple and clearly identified with the controls with which they were associated.

The oxygen flowmeter was to be located on the right-hand side of the flowmeter bank and was to be delivered downstream of all other gases, so that in the event of a leak, oxygen would be delivered in preference to other gases. The oxygen flow control was to be fluted while the other controls were to be round, thus providing instant tactile identification of the oxygen control. An oxygen analyzer would indicate the oxygen concentration in the gas mixture being delivered to the patient, and an alarm would sound should the level fall below the preset minimum. Non-interchangeable Diameter Index Safety System (DISS) inlet fittings were to be used to attach the flexible hoses from the gas pipeline system to the anesthesia machine. Agent-specific filling systems were designed for the vaporizers, to prevent them from being filled with an incorrect agent or being overfilled. The vaporizer control was to open in the same direction of rotation as the gas flow controls.

Because of the wide range of engineering items that are dependent upon human factors, these committee members formed the Association for the Advancement of Medical Instrumentation Human Factors Engineering Committee. The author served as the co-chairman. By 1988, the committee produced the Recommended Practice on Human Factors Engineering for the Design of Medical Devices.

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The Evolution of Intraoperative Transesophageal Echocardiography

YASU OKA

Abstract

In this article, the development of intraoperative transesophageal echocardiography (TEE) is reviewed. It took two decades to develop the present clinical applications of TEE. This modality will continue to serve as a monitor and diagnostic tool to ensure better care of patients in the operating room and the intensive care units.

Key Words: TEE, transesophageal echocardiography, intraoperative TEE.

LORD BYRON STATED THAT "the best of the future is the past." With this in mind, it may be meaningful and helpful to retrace the historical development of intraoperative transesophageal echocardiography (TEE).

In the early 1960s, during the developmental stages of cardiac surgery and anesthesia, the care of patients in the operating room and during recovery was challenging. There were no mentors to teach us, nor were books available to look up the necessary information. We had to learn how to care for patients from our daily experiences in the operating room and intensive care units. There were no simple and reliable monitoring systems to measure hemodynamic changes.

Although many of these problems were resolved by the latter half of the 1970s, it became apparent that the techniques for measuring cardiac output and various pressures were inadequate to assess rapid changes in ventricular compliance and ventricular performance which occurred during coronary artery bypass surgery. To solve this problem, a great deal of research was required to obtain information on ventricular dimensions and volumes. At about this time, transthoracic echocardiography was recognized by our cardiology colleagues as an effective method for assessing left ventricular dimensions and performance. In 1978, we employed epicardial echocardiography using a commercially available M-Mode transthoracic probe to evaluate left ventricular function in patients undergoing coronary artery bypass surgery. This technique was useful but quite cumbersome and suffered from a number of inherent problems:

1. The surgeon was forced to interrupt the operation.
2. It was technically difficult to position the probe at the same site and with the same angle relative to the heart for repeated, accurate measurements.
3. There was a risk of infection.

For these reasons, we were constantly searching for a better, simpler approach for determining ventricular dimensions and volumes.

In August 1978, I met Dr. Masayuki Matsumoto, an experienced echocardiographer in the Department of Cardiology at Osaka University, while he was a visiting associate in the laboratory of Dr. Edmond Sonnenblick of the Department of Cardiology at the Albert Einstein College of Medicine. When I met him again in October, he had not yet found a research project and was somewhat frustrated. To comfort him, I invited him to my house for dinner one evening. During an after-dinner conversation on our study of intraoperative epicardial echocardiography, he casually mentioned the work on transesophageal echocardiography by Frazin et al. in 1976 (1), saying that this approach was abandoned because patients found it very difficult to swallow a probe. I suddenly had a flash of inspiration to combine our esophageal stethoscope, which we had been using for anesthetized patients, and an M-Mode echocardiographic probe in the hope that we would be able to determine the ventricular di-

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mensions and volumes. Without delay, I fabricated a handmade transesophageal probe based on an already available probe. The very thin cord was stiffened with a #4 sternal wire and covered with a vinyl esophageal stethoscope catheter. Using this handmade probe, we were able to determine the left ventricular dimensions and calculate the systolic and diastolic volumes, cardiac output and ejection fraction in a 65-year-old woman undergoing mitral valve repair; diastolic and systolic volumes were calculated according to the formula suggested by Teichholz (2). I cannot forget the great joy that we had from the result of this study. This study was published in the *New York State Journal of Medicine* in January 1979 (3). Thereafter, I stiffened this probe even more. Within 6 months, we completed the next study, entitled "Application of Transesophageal Echocardiography to Continuous Intraoperative Monitoring of Left Ventricular Performance." This work was reported at various meetings in the U.S., Europe and Japan (4 – 10) and published in the *American Journal of Cardiology* in July 1980 (11). Following this study, Dr. Matsumoto left us for the Department of Cardiology in the University of Hamburg, where he continued his M-Mode TEE study. He reported his work on stress echocardiography in 1982 (12).

I continued to work on M-mode transesophageal echocardiography in cardiac surgical patients. From our previous studies, we recognized the limitation of M-mode TEE; therefore, we searched for an engineer to help us design a phased array TEE probe attached to a gastroscope. In the summer of 1980, I had an opportunity to visit the president of a Japanese gastroscope company in New Jersey. I discussed my publications and requested engineering support to design and create the TEE probe. This association ended in great disappointment. In 1982, my friend, Dr. Michio Morio, professor and chairman of the Department of Anesthesiology at Hiroshima University, obtained an M-mode TEE probe attached to a fiberoptic bronchoscopy. Using this probe, we continued our study of left ventricular function and the detection of intracardiac air bubbles (13, 14).

While I was searching for engineering help, Souquet and colleagues in Hamburg, Germany, introduced the electronic phased-array transducer in 1982, which represented a definitive breakthrough for the transesophageal approach (15). The initial application of this probe was described at the University of San Francisco for intraoperative monitoring of regional myocardial function in high-risk, non-cardiac surgical patients and the recognition of intracardiac air during neurosurgical procedures (16).

During the period 1983 – 1986, our research work on TEE failed to show much progress because of the lack of engineering help. In the winter of 1986, I met the chairman and chief operating officer of Toshiba America Co. in New York City. He came to the anteroom where I sat, carrying reprints of my publications and asked me what he could do to help me. I explained my work on TEE and told him that I needed engineering help to develop a clinically useful TEE probe. I remember I had a hard time convincing him to support my undertaking. Although he was a dynamo in the business world, he was not well versed in medicine. After a long discussion of the project, I showed him my article in the February 1980 issue of *Anesthesiology News* (5) entitled "New Device Will Facilitate Intraoperative Cardiac Monitoring." He suddenly showed interest in my work and promised that he would contact the responsible individuals in the medical division of Toshiba, Tokyo. In April 1987 (during the best time for cherry blossoms in Tokyo), I met two senior engineers in the medical division of Toshiba Company. That August, we signed an official agreement regarding cooperative development of Toshiba Ultrasound Products for TEE in the operating room and intensive care unit.

We continued to have a meaningful association with Toshiba Company, which led to the most productive years of our TEE research and research fellowship program. Late in the 1980s, color flow mapping combined with higher resolution imaging was introduced to TEE and used by a number of investigators. This led to an explosive and widespread increase in the application of TEE in anesthesiology, cardiac surgery, and cardiology. In 1989, mechanically driven high-frequency transducers with an annular array providing both high resolution and the capability for continuous wave Doppler interrogations were developed (17, 18). Omoto et al. introduced biplane TEE in 1989 (19) to overcome the lack of versatility associated with imaging structures only in the transverse plane. Biplane TEE employed two phased array transducers (one imaging in the transverse and one in the longitudinal plane) that were mounted at the tip of a gastroscope. Each transducer had 32 elements and operated at 5 Mhz. The distance between the centers of the two transducers was 1 cm. As a consequence, minimal repositioning of one transducer was required to visualize exactly the same cardiac segment. To overcome the problem of repositioning, a phase array matrix was developed which allowed orthogonal biplane scanning from one transducer which was kept at constant position. At that time our new chairman, Dr. Paul Goldiner, strongly supported this corporate alliance as well as our TEE research.

By 1990, many companies began to produce commercially available 2D color Doppler biplane TEE probes with improvements in echo systems. In 1992, Pandian et al. reported 3D-4D TEE in humans using a computed tomographic imaging probe (20); however, this modality is not yet commonly used.

It took two decades to reach the present status of intraoperative TEE. There is no doubt that the application of this technology in cardiac anesthesia was a turning point in the care of patients in the operating room and intensive care unit. I believe that this technology will continue to serve as a monitor and diagnostic tool to ensure the superior care of patients in cardiac surgery. Its applications will be extended to other patients in critical conditions. I am extremely pleased to have witnessed the numerous innovative and challenging developments of this modality by so many creative investigators.

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Neuroanesthesia at The Mount Sinai Hospital

Henry C. Tausk, M.D.[1], and Irene P. Osborn, M.D.[2]

Abstract

The practice of neuroanesthesia at the Mount Sinai Medical Center focused initially on clinical practice, followed by specialization. This article presents a brief history of the division and a description of the areas of interest, presentations, and publications that have originated there.

Key Words: History of anesthesia, neuroanesthesia.

The term "neuroanesthesia" is much younger than our department. Surgeons and their assistants had been providing pain relief for neurosurgical patients for many years before the Department of Anesthesiology existed and before physicians began to specialize in anesthesiology. In 1916, Dr. Charles A. Elsberg, the leading neurological surgeon at The Mount Sinai Hospital, stated (1): "If the laminectomy is done in the cervical and upper dorsal regions, anesthesia by intratracheal insufflation is the best and simplest method." At this time the vast majority of general anesthetic procedures were performed using open mask ether administration.

One can identify three "eras" in the evolution of anesthesia for neurosurgery at our institution over the past 50 years:

From 1950 – 1964 most members of the Department of Anesthesia probably administered anesthesia during neurosurgical procedures according to an informal roster of rotation. No copies of such a roster have survived, nor do we know whether the individual anesthesiologist's preferences were considered. At that time, it was customary for surgeons (implicitly for neurosurgeons) to indicate their choice of anesthesiologists; in the prevailing circumstances of surgical private practice, their requests were usually granted.

The second period started around 1968, when some anesthesiologists began spending more and more time in the neurosurgical operating room, becoming the "in-house" specialists for the neurosurgical procedures. The anesthesiologists who began this specialization were Drs. Alex Goldblat, Raymond Miller and David Chadwick. At the same time, a teaching program was started. The regular anesthesia training consisted of a two-year residency with a minimal, informal rotation in the neurosurgical operating room. For the first time, specialized training was offered to select candidates as a third year of residency. Those who entered the program spent a whole year in the neurosurgical operating room. They were expected to participate in some aspects of the postoperative care and encouraged to attend neurosurgical grand rounds. The first resident to hold this third-year position was Dr. Boris Mogos, in 1969 – 1970. Afterwards, Dr. Mogos specialized in neurosurgical anesthesia in the hospitals of the Albert Einstein College of Medicine (AECOM), where he was the divisional director of Neuroanesthesiology for many years. The same Dr. Mogos, nineteen years later, made his wisdom available to his young colleague, Dr. Irene Osborn, at AECOM. After graduation from his own neuroanesthesia subspecialization training, Dr. Henry Tausk became an attending anesthesiologist at The Mount Sinai Hospital, in place of Dr. Chadwick, in 1971.

It was at this time that the "Society for Neuroanesthesia and Neurological Critical Care" was organized, and the term "neuroanesthesia" started to be widely used. Dr. Raymond Miller and Dr. Tausk joined the new subspecialty group at its inception during the 1972 annual meeting of the American Society of Anesthesiologists. By this time Dr. Goldblat had, unfortunately, passed away.

The third period began in 1984, when the Division of Neuroanesthesia was formally constituted within the Department of Anesthesiology. The first director of this division was Dr. Tausk. After his retirement from this position in 1990, acting directors ran the division. The first was Dr. Neil Bodner. After Dr. Bodner's departure, Dr. Raymond Miller assumed this position in addition to his responsibilities as vice-chairman of the department. In 1998 Dr. David Adams, coming from the Columbia-Presbyterian Medical Center, was named director of the Division of Neuroanesthesia.

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During all these years the division was active in providing anesthesia services to the departments of Neurological Surgery and Neuroradiology. Providing these services for the latter could be difficult. During the 1960s and 1970s, pneumoencephalography was a frequently performed procedure. We were often asked to anesthetize patients who were strapped into a rotating chair and moved repeatedly into the head-down position. Maintaining the tracheal tube in position, hyperventilating the lungs, and properly supporting the cardiovascular function in our anesthetized patients while these "calisthenics" were performed was a challenge for the neuroanesthesiologist.

Research

During most of these 50 years (until 1984), the general anesthesia services as well as the neuroanesthesia services were provided almost exclusively by a staff consisting of voluntary physician anesthesiologists. Due to these circumstances, the emphasis was always on clinical work and clinical training of residents, while research was a lower priority. Almost all academic pursuits were clinically oriented. Research studies were few in number and hampered by clinical responsibilities. Nevertheless, we made some academic contributions, which we will now survey briefly.

From the very beginning of the subspecialization, Mount Sinai anesthesiologists were concerned with certain aspects of neurosurgical operations. One area of interest was "incidental hypothermia" due to the prolonged operating times; Drs. Goldblat and Miller first described this problem in 1972 (2), and a possible solution was published some years later by Drs. Tausk, Miller, and Roberts (3). The effects of anesthesia during prolonged neurosurgical procedures were presented by our division in 1980 (4).

During the second period, while we were striving to provide specialized neuroanesthesia, one of our main problems was patient monitoring. Intra-arterial pressure monitoring and blood gas determinations were still in their infancy. Mean arterial pressure was measured by transducing intra-arterial pressure from an indwelling peripheral arterial cannula via a column of air using a simple pressure gauge: the column of air between the arterial blood and the gauge served as a buffer, and the pulsations of the arterial blood were indicated on the gauge. A three-way connector allowed for flushing of the system every five minutes with heparinized saline. This primitive device also allowed for easy arterial blood sampling. Our description of this system, on the occasion of an international meeting of developing countries, attracted widespread interest. For a certain period of time we had a blood-gas analysis apparatus just outside the operating room. This device, which necessitated calibration before every measurement, was quite cumbersome and its use was time-consuming. After it broke down, a resident or an attending physician personally took every sample of arterial-blood gas to the intensive care unit (ICU) laboratory for rapid determinations.

A major breakthrough in our monitoring resulted when Dr. Malis built a custom-made, transducer-based pressure monitor in the early 1970s. It had the capability to transduce three pressures: systemic arterial pressure, central venous pressure, and intracranial pressure. The monitor was calibrated each morning using a 760-mm mercury tube and had to be re-calibrated approximately every six hours. Since the apparatus was the size of a huge cupboard, it was nicknamed "the Monster." Even with these limitations, it was a big step forward in perioperative patient monitoring.

Another major development in patient monitoring occurred in the early 1980s, when we began using electrophysiologic monitoring. Our first device was the cerebral function monitor (Critikon, Inc., Tampa, FL), which was one of the earliest devices developed to simplify EEG monitoring in the operating room. It was a microprocessor-based, single-channel unit, which gave information on global cerebral activity. We used it to measure depth of anesthesia. Soon thereafter we obtained a Nicolet monitor (Nicolet Biomedical Instruments, Madison, WI) and began monitoring somatosensory evoked potentials (SSEPs) in an effort to evaluate the integrity of the central nervous system. A waveform is generated by repetitive stimulation of peripheral sensory nerves. The unchanging shape (amplitude) and speed of conduction (frequency) of the waveform demonstrate that the neurologic pathway is intact. The goal was to diagnose and prevent possible neurological injury when anesthetized patients are placed in the upright sitting position.

We also documented our interest in patient monitoring, in papers presented at meetings of professional societies (5 – 7). For a number of years (1984 – 1987), our department was instrumental in conducting workshops on patient monitoring at the Annual Postgraduate Assembly of the New York State Society of Anesthesiologists.

Our division was also interested in the effects of certain pharmacological agents used during neurosurgical procedures. We studied the effects of neuroleptic agents on cerebrospinal fluid pressure (8). In the 1980s, induced controlled hypotension was a frequent requirement for neurosurgical operations. To achieve it, trimethaphan camsylate, and subsequently sodium nitroprusside, were used. Both drugs were potent and effective hypotensive agents, but both had significant undesirable side effects. We decided to try a prefixed combination of the two drugs. We found that when infusing the mixture, we were able to maintain proper hypotension when extremely low amounts of the drugs were administered, thus avoiding the deleterious side effects. At first, we recorded our efforts in a letter to the editor (9), but at a later date we revisited the problem and published our findings more fully (10).

During the operative career of Dr. Leonard Malis, due to his special interest and expertise, approximately 20% of our cases were performed with the patient in the sitting position. Surgery performed in this way allows for access to the posterior fossa and the cervical spine. It also allows the surgeon an "anatomical" view and results in less bleeding, because of reduced venous pressure. But despite these distinct advantages, the sitting position also poses risks. Patients tend to become hypotensive with decreased venous return and the loss of sympathetic tone. The combined circumstances of the upright position, non-collapsible cerebral veins and the "head above the heart" create potential for air entrainment into the venous system. Anesthetic management requires both monitoring of hemodynamics as well as attention to possible venous air embolism. The anesthetic considerations of the sitting position were described by our group in various publications (11 – 13).

In the past decade, our clinical practice has shifted toward the neurosurgical interests emphasized by Dr. Post, e.g., pituitary surgery, neurovascular surgery, stereotactic surgery and interventional neuroradiology, so the sitting position for posterior fossa surgery is now seldom necessary. Other changes in general neurophysiologic thinking have led to the 1990s being called the "decade of the brain." While we had previously monitored and emphasized the control of intracranial pressure, modern practice management now stresses the maintenance of adequate cerebral perfusion.

Neurosurgical practice is now closely connected to refinements in the new procedures of stereotaxis with MRI targeting. Interventional neuroradiology is a dramatically expanding field, which offers "minimally invasive" adjuncts to complex cerebrovascular problems. Neuroanesthesiologists are increasingly involved in these procedures. Electrophysiologic monitoring is on its way to becoming a routine intraoperative neurosurgical practice. In addition, mild hypothermia, as a method of cerebral protection during cerebral ischemia, has gained wide acceptance again. This use of hypothermia has come almost full circle from the days when we tried to avoid it. Volume replacement and "re-hydration" are carefully reconsidered, with new ideas in quantitative and qualitative terms. Finally, new anesthetic agents like propofol and synthetic opiates are transforming our anesthetic techniques, allowing for reliable emergence and neurologic evaluation after the (still prolonged) operative procedures.

Future developments in neuroanesthesia at our institution cannot be predicted, but based on the preceding 50 years, we are optimistic about being able to continue serving not only our patients but also the progress of knowledge.

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The Surgical Intensive Care Unit of The Mount Sinai Hospital:

A Brief History Focusing on Contributions to Academic Critical Care Medicine and Excellence in Patient Care

Andrew B. Leibowitz, M.D.

Abstract

The Mount Sinai Hospital Surgical Intensive Care Unit (SICU) was founded in 1969. Drs. William Shoemaker and Christopher Bryan-Brown were the first directors. Since it was founded, the SICU has been an integral part of the Mount Sinai Medical Center, providing a wide variety of clinical services including critical care, central line placement, and nutritional consultation. As one of the largest training programs in the United States and a frequent contributor to the medical literature, the SICU has also played a vital role in academic critical care medicine.

Key Words: Critical care medicine, intensive care unit, history.

Modern critical care medicine was born in the late 1960s. The original multidisciplinary medical and surgical intensive care units (ICUs) were based on medical care provided in cardiac and cardiac surgical intensive care units, as well as in recovery rooms. In April 1970, The Mount Sinai Hospital renovated the Falk building, originally completed in 1931, and established its first Surgical Intensive Care Unit (SICU), hence the name "Falk ICU." The Society of Critical Care Medicine, the world's leading critical care organization, was founded that same year. The Falk building admirably housed the initial 21-bed unit with two additional research beds for nearly 20 years.

Dr. Christopher W. Bryan-Brown, The Mount Sinai Hospital's first intensivist and current vice-chairman of Anesthesiology at Montefiore Hospital Medical Center, recalled that (1), "much of the early opposition to recovery rooms and ICU's in the United States came from hospital administrators. They did not wish to find the funds to train and maintain skilled staff, whose services previously have been provided haphazardly but at others' expense. In 1969, I witnessed Leslie Rendell-Baker, the Chairman of Anesthesiology, and Alan Kark, the Chairman of Surgery, at the Mount Sinai Medical Center in New York take on a very reluctant hospital administration for a full-time salaried physician to work in a newly proposed ICU. The administrative powers contended that the ICU could be run by an anesthesiologist who would perform his duties there when not occupied in the operating room. Confronted with data from other prestigious institutions nationwide, the administration was convinced, and I began my career as a full time salaried ICU director of a multispecialty unit."

Dr. William Shoemaker joined Dr. Bryan-Brown soon thereafter. Dr. Shoemaker was the first editor of the journal *Critical Care Medicine*, the author and editor of the first textbook dedicated to critical care medicine as a separate discipline, and a researcher par excellence. He authored several hundred peer-reviewed publications over the course of his career, the focus of his research being the physiologic response to injury and the potential to manipulate physiologic responses in order to improve outcome. Almost single-handedly, he built upon the basic physiologic principles of oxygen delivery and consumption, and developed the ideas of pathologic supply dependency as an entity and supranormal oxygen delivery as a treatment mode. These latter two concepts have been at the heart of a long controversy within the critical care

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community, with ardent supporters and equally impassioned detractors. Interestingly, the current SICU staff is entirely in the camp of the impassioned detractors.

Dr. Koing-Bo Kwun, who is currently professor and chairman of surgery in Yeungnam University Hospital in Korea, followed Drs. Shoemaker and Bryan-Brown as director. I trained under the next Director, Dr. Thomas Iberti, who had an untimely death at age 40 in 1993. The current director, Dr. Ernest Benjamin, first came to Mount Sinai as an anesthesiology resident via Haiti and France at about the same time that Dr. Iberti became the director. Thus, in the 30 years since the SICU was founded, there have been only five directors. I think this has accounted for its consistency in personality and approach, stressing collegiality, excellence in patient care regardless of the time of day or night, education of medical students, residents and fellows, and research.

Under Dr. Iberti's leadership, the first critical care fellows were trained. They were Drs. David Gentili (an internist), George Gabrielson (an anesthesiologist), and Kathleen Kelly (a surgeon). Dr. Gentili eventually returned to his home country of Venezuela and became director of an intensive care unit; Dr. Gabrielson remained at The Mount Sinai Hospital and is an associate clinical professor of anesthesiology and director of liver transplantation anesthesia; and Dr. Kelly went on to become the director of the SICU in Morristown Memorial Hospital in New Jersey. Since that time, the Mount Sinai Critical Care Fellowship Program has grown under the direction of Dr. Oropello and myself. It has been approved by the American Boards of Internal Medicine and Anesthesiology. To date, more than 100 fellows have graduated and our program is one of the largest in the country. We also participate in the training of the pulmonary critical care fellows who are in the Pulmonary Critical Care Division of the Department of Internal Medicine directed by Dr. Alvin Teirstein.

Over this past 30 years, the Surgical Intensive Care Unit has been moved several times to accommodate its growth. It is now in the new Guggenheim Pavilion which was designed by the world renowned architect I.M. Pei. The staff has grown from the original two attending physicians to five, along with two research nurses, a database coordinator, a computer network administrator, a biochemist, and two secretaries. Our fellows rotate through the City Hospital Center at Elmhurst, the Bronx Veterans Administration Medical Center, and Englewood Hospital in New Jersey. One of our graduates is in charge of the SICU at each of these hospitals. At The Mount Sinai Hospital, we cover the SICU, the neurosurgical intensive care unit, which is now a stand-alone facility, the surgical nutrition support service and the central venous access service. Thus, our clinical services touch upon the lives of literally thousands of patients yearly.

The following short review will trace some of the contributions made to critical care by the Mount Sinai team during the past 15 years.

Pulmonary artery catheterization was a technique developed for clinical use during the 1960s that became commercially available in 1970. Originally, pulmonary artery catheters were developed to assist in the management of patients experiencing myocardial infarction complicated by hypotension and congestive heart failure. However, medical and especially surgical ICUs embraced this invasive technologic advance with such exuberance that one author of a very popular handbook (2) concluded that "the pulmonary artery catheter is not just important for the specialty of critical care, it is responsible for the specialty of critical care." Early users of this device were discouraged because of the time required to place it and the often life-threatening arrhythmias experienced. However, in 1985, Iberti and Benjamin published a study demonstrating the safety and speed with which these catheters could be inserted, thus assuring their general acceptance by the critical care community (3).

Since then, complications of central venous access in general, and pulmonary artery catheterization in particular, became a favorite subject of reporting by the SICU staff. Physical complications that were reported for the first time, or in case series, included delayed (4) and bilateral chylothorax (5), delayed bilateral pneumothorax (after a single puncture) (6), malposition outside of the central circulation (7), and position in a left-sided superior vena cava (8). Later, Dr. Oropello and the SICU group postulated a possible unrecognized complication of vessel dilation, and recently have been in consultation with industry to reduce this risk (9). These publications have been widely referenced and some are included on the package inserts of the commercially available central venous access kits. Furthermore, Dr. Kwun was among the first, if not the first, to report percutaneous cannulation of the brachial vein using Seldinger's technique (10). This is now the predominant percutaneous method of inserting central venous catheters from an extremity vein.

More important, in 1984, Dr. Iberti, recognizing the high incidence of avoidable complications from central venous catheterization and opposing the "see one, do one" approach to teaching invasive procedures, established the first and only ICU-based vascular access service. Now known as the Central Venous Access Service, it places approximately 1,200 central venous catheters per year in non-ICU patients, with a major complication rate, including pneumothorax, of less than 0.5%. This service, located within the SICU, operates out of a procedure room equipped with its own fluoroscopy unit and ultrasound vessel finder probe. It is staffed by a dedicated full-time nurse. To my knowledge, no other center has this service, or any reasonable facsimile. In its 16 years of existence, it has prevented innumerable morbidities and mortalities.

Pulmonary artery catheters were used to obtain physiologic information that was previously unavailable and impossible to ascertain by other means. By 1988, however, there was a growing suspicion in the critical care community that the overall outcome of patients did not seem to be significantly improved with these data. Dr. Iberti suspected that part of the problem was that physicians and nurses did not understand how to use the device. He recruited me to assist him in developing a short exam of multiple-choice questions to test this hypothesis. We formed the Pulmonary Artery Catheter Study Group, which included several leading physicians from the United States and Canada. In what has subsequently been acknowledged as a landmark study, the exam was administered to 496 physicians in 13 hospitals in these countries, to assess their knowledge and understanding (11). The mean test score was 67% correct. Astoundingly, there was a general misunderstanding and lack of knowledge about some of the most basic information required to use this device safely and effectively. For example, from a hard copy pulmonary artery wedge pressure tracing, only 47% of the respondents could correctly identify the wedge pressure. This was big news, big enough to warrant a story in *The Wall Street Journal*. Subsequently this same questionnaire was administered to critical care nurses (12, 13), and European physicians (14), and as a take-home exam to Society of Critical Care Medicine members (15). Each time this exam was administered, Dr. Iberti's original hypothesis was confirmed — that the personnel in charge of inserting and maintaining pulmonary artery catheters, and interpreting the information derived, lacked the basic knowledge and skill to do so. This led to standardized education programs for physicians and nurses which mandate that any outcome studies examining pulmonary artery catheterization ensure that the physicians and nurses can correctly use and interpret information gained from this device.

This academic achievement led to my involvement in the Society of Critical Care Medicine Consensus Committee (16) for which I wrote the "chapter" on perioperative pulmonary artery catheterization with Dr. Beilin, another anesthesiology staff member with whom I have frequently collaborated (17).

The SICU's latest publication concerning pulmonary artery catheterization examined whether standard central venous and atrial pulse tracings recorded by bedside monitors would detect a, c and v waves. It was concluded that, for the most part, these waveforms were not routinely detected by the common strip-chart recorders (18). Hence, many of the long-held beliefs regarding the observation and interpretation of these waveforms are probably based upon theory and laboratory monitoring, not bedside clinical practice.

As a result of our dissatisfaction with pulmonary artery catheterization, we explored other monitoring devices. Gastric tonometry looked hopeful to many in the critical care community in the early 1990s, but our research and that of others has significantly dampened enthusiasm. A case report of a patient with gastric ischemia pointed out the limitations of this device (19) and a subsequent book chapter written by members of the SICU staff reviewed its limitations and concluded that it was not a useful clinical adjunct (20). Although tonometry is commercially available and much easier to use now, only a handful of centers are using this device.

Just before he died, Dr. Iberti began collaborating with Dr. Martin Goldman, the director of noninvasive cardiology, whose facilities are in close proximity to the ICU. Dr. Goldman has long been recognized as an expert echocardiographer and a leader in transesophageal echocardiography. Transesophageal echocardiography is the echocardiographic method of choice for critically ill patients because of the ease with which a tracheally intubated patient may be examined and the superior quality of images obtained compared to transthoracic echocardiography. The utility of transesophageal echocardiography (TEE) performed on SICU patients by intensivists who were not expert echocardiographers was explored. After Dr. Iberti's death, Dr. Benjamin and his staff pursued this line of investigation. This research culminated in a publication that demonstrated the utility of TEE and, more important, its potential superiority to pulmonary artery catheterization (21). We coined the term "limited scope TEE" to refer to examinations done primarily to evaluate global left ventricular function and filling that could be performed by intensivists after a relatively short period of training. This area of monitoring is being explored by a growing number of intensivists worldwide. More recently we participated in a multicenter study investigating the utility of a new miniature probe the size of a standard naso-gastric tube that may change the face of ICU monitoring in years to come (22). This probe can be inserted easily and left in place for prolonged periods, yielding excellent continuous echocardiographic images.

The Surgical Intensive Care Unit staff was also among the first to report on a wide variety of clinically useful approaches and techniques that had been unrecognized or had only been practiced sporadically prior to publication. These publications in peer-reviewed journals included the utility of bedside percutaneous gastrostomy tubes (23), use of bedside diagnostic laparoscopy (24), continuous infusion of verapamil for control of supraventricular arrhythmias (in the pre-diltiazem era) (25), the common occurrence of benign thrombocytopenia after abdominal surgery (26), and the prevalence of depression among ICU patients (27).

We were the first to report a new, easy, inexpensive, and effective way to monitor intra-abdominal pressure using an indwelling Foley bladder catheter (28, 29). This method can be used when increased intra-abdominal pressure is suspected and for the diagnosis of an intra-abdominal compartment syndrome.

In 1990, we reported that hyperlactatemia could be present even in the face of a normal anion gap (30). Until this publication, traditional medical teaching was that, without an elevated anion gap, hyperlactatemia was unlikely to be present and testing for it was not cost effective. However, this teaching did not take into account the multitude of simultaneous acid-base abnormalities that critically ill patients have and the intravenous infusion of fluids which may be lower or higher than the patient's arterial pH. This publication was also among the growing body of intensive care literature demonstrating the futility of trying to apply general medical principles derived from the outpatient setting and from patients suffering from single-organ dysfunction, to patients with multi-organ dysfunction on life support in the intensive care unit.

We were the first to show that the administration of alprostadil does not prevent renal dysfunction in liver transplant recipients (31). This was our first randomized double-blind study performed entirely within the confines of our own intensive care unit. Prior to this report, alprostadil was widely used and variously reported to decrease intraoperative bleeding, reduce postoperative renal dysfunction, reduce mortality and decrease the length of stay (32). Our clinical impression that this drug was highly overrated was widely challenged, but a follow-up study confirmed this conclusion. The now infrequent use of this drug in liver transplantation has resulted in significant cost-savings (33).

We also have developed an animal laboratory and biochemical research facility currently under the direction of Dr. Manasia. Some of the lines of investigation have included the monitoring of shock (34–37), utility of novel therapies (38–40), measurement of extravascular lung water using bioimpedance (41) and the measurement of molecular compounds to indicate the extent of reperfusion injury (42). The multidisciplinary nature of these studies requires the participation of colleagues from medicine, plastic surgery and transplant surgery.

Critical care medicine in the 1990s will probably best be remembered for the hype and hope that monoclonal antibodies would be the magic bullet to markedly reduce mortality from sepsis and septic shock. We, along with virtually every other major academic unit in the country, participated in these multicenter investigations with great hope, oftentimes as one of the leading recruiters of patients (43–45). Unfortunately, to date, all of these investigations have yielded disappointing results and the "magic bullet," if there is one, remains elusive. Most recently, we participated in the investigation of insulin-like growth factor for the treatment of acute renal failure (46). I believe that the amount of research on "growth factors" will grow exponentially in the coming decade.

However, something has changed in our unit and probably in critical care medicine in general. Compared to 20 years ago, despite the lack of any single demonstrable advance, the outcome from the Adult Respiratory Distress

Syndrome has improved dramatically, and other critical care entities have seen a subtler decline in mortality. For instance, in 1998 – 1999, of 42 patients who required hemodialysis and mechanical ventilation, 27 (64.3%) survived to hospital discharge. Perhaps more impressively, of 49 patients who spent more than 30 days in the ICU, 27 survived to hospital discharge (47%). Although I don't have comparative data from our SICU 10 years ago because an electronic database wasn't in place then, these survival rates greatly surprise most non-ICU physicians. I attribute these remarkable recovery rates to a large variety of factors including: (a) the persistent, aggressive, uniform nature of care our team delivers day in and day out; (b) the stress we put on each individual patient's outcome and not on our unit's length of stay or overall performance compared to some arbitrary benchmark; (c) the pioneering and judicious use of continuous veno-venous hemofiltration; (d) the onsite presence of an ICU fellow and the continuous availablility of an ICU attending regardless of the time of day or night; (e) the excellent nursing and support staff and, lastly, (f) the presence of state-of-the-art technology for which we have various hospital administrators and department chairmen to thank. This last factor is probably the most tenuous of all, given the ubiquitous "cut costs now" approach that has permeated our entire health care system.

Looking forward, as the Surgical Intensive Care Unit enters the new millennium, I hope that its achievements over the next 30 years approach those of our past 30 years. That alone would be a truly remarkable accomplishment.

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Anesthetic Implications of Myasthenia Gravis

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Abstract

Myasthenia gravis is a disease of great significance to the anesthesiologist, because it affects the neuromuscular junction. Many patients with this condition are treated by surgical thymectomy, using techniques developed by Mount Sinai physicians, including Dr. Paul Kirschner, Dr. Alan E. Kark, and the late Dr. Angelos E. Papatestas. The authors review the anesthetic considerations in the management of patients with myasthenia gravis who are undergoing thymectomy and other surgical procedures.

Key Words: Myasthenia gravis, anesthesia, thymectomy.

Epidemiology and Pathophysiology

MYASTHENIA GRAVIS (MG) is an autoimmune disease characterized by weakness and fatigability of skeletal muscles, with improvement following rest. It may be localized to specific muscle groups or it may be generalized. The incidence is 50 – 142 cases per million population (1). MG is caused by a decrease in the numbers of postsynaptic acetylcholine receptors at the neuromuscular junction (2), which decreases the capacity of the neuromuscular end-plate to transmit the nerve signal. Initially, in response to a stimulus resulting in depolarization, acetylcholine is released presynaptically. In MG, the number of activated postsynaptic receptors may be insufficient to trigger a muscle action potential (3). Further, with repeated stimulation, the decline in release of acetylcholine correlates with the characteristic fatigability (4).

Presentation and Diagnosis

The characteristic presentation of MG is fatigability of voluntary muscles. Most commonly, the eyelids and extraocular muscles are involved. Bulbar involvement may be manifested as difficulty in chewing and swallowing. Eighty-five percent of myasthenic patients go on to develop generalized weakness; some develop respiratory failure. Thymoma is present in 10 – 15% of patients with MG (5). In a now classic paper, Osserman and Genkins, both physicians at The Mount Sinai Hospital, published a clinical classification of myasthenia gravis that is still in widespread use (6).

The diagnosis of MG can be confirmed by several tests. The anticholinesterase test is positive if strength improves with inhibition of cholinesterase. When cholinesterase is inhibited, more acetylcholine is available to interact with the decreased number of postsynaptic receptors, increasing the likelihood of adequate end-plate depolarization. Edrophonium (Tensilon®) is usually administered intravenously in small (2 – 8 mg) doses for this test. This test was introduced and popularized by Dr. Osserman (7). Electromyography is also used in the diagnosis of myasthenia. Repetitive stimulation of a peripheral motor nerve leads to decreasing responses by the innervated muscle in a patient with MG. The presence of anti-acetylcholine antibodies in the serum, as detected by radioimmunoassay, is diagnostic of MG. Such antibodies may not be detectable, however, in all patients with mild symptoms at presentation.

Treatment

Treatment of MG may be medical or surgical, utilizing one of three approaches: anticholinesterases (medical), immune suppression (medical), or thymectomy (surgical).

Improving neuromuscular transmission by means of anticholinesterase agents is the most common approach. Pyridostigmine (Mestinon) in a dose of up to 120 mg p.o. every 3 hours is

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used because it is tolerated well orally, with few muscarinic side effects, and has a relatively long duration of action. Pyridostigmine 30 mg orally is equivalent to 1 mg intravenously or intramuscularly.

Immune suppression is directed at preventing or attenuating the destruction of acetylcholine receptors at the motor end plate (8). Corticosteroids, which cause immune suppression, will improve the condition of most myasthenics (9). Those who do not respond or who cannot tolerate the side effects may respond to azathioprine 2.5 – 3.5 mg/kg. Cyclosporine has been used in patients with MG (10) and compares favorably with azathioprine (11).

For patients with severe bulbar symptoms or respiratory compromise (myasthenic crisis), plasmapheresis is used (12). Significant improvement occurs over days, with decreased dependence on ventilatory support (13). The presumed mechanism is the removal of antibodies, allowing receptors to proliferate. Immune globulin given intravenously has been used to treat myasthenic crises when plasmapheresis cannot be used. Its use has been associated with good short-term improvement (14).

Thymectomy is used to treat MG, but the mechanism of its action remains speculative. Antibody titers decrease with clinical improvement (15). Suggested mechanisms include removal of antigenic stimulus by the removal of myoid cells or alterations in immune regulation by removal of the thymus. For an up-to-date history of surgery of the thymus gland, as well as speculation on the future, the recent review by Kirschner (16) is recommended reading.

Anesthesia Considerations — Preoperative Evaluation and Preparation

Preoperative evaluation of the MG patient includes review of the severity of the patient's disease and the treatment regimen. Specific attention should be paid to voluntary and respiratory muscle strength. The patient's ability to protect and maintain a patent airway postoperatively may be compromised if any bulbar involvement exists preoperatively. The ability to cough and clear secretions may be compromised as well. Respiratory muscle strength can be quantified by pulmonary function tests (negative inspiratory pressure and forced vital capacity). These tests may be necessary as a reference to determine the optimal conditions for extubation postoperatively as well as the need for postoperative mechanical ventilation (17, 18).

If a thymoma presents an anterior mediastinal mass, intrathoracic airway or vascular obstruction may occur upon the induction of anesthesia. Flow-volume loops may be indicated preoperatively. Maximal inspiratory and expiratory flow-volume loops obtained with the patient in the supine and upright positions will measure the extent of the respiratory impairment as well as whether the impairment is fixed or dynamic.

The preoperative management of the myasthenic patient will be influenced by the surgical procedure and the preferences of the surgeon and the anesthesiologist. Some choose to omit anticholinesterase on the morning of surgery, to decrease the need for muscle relaxants (21), whereas others continue its use for psychological support of the patient. If the patient is poorly controlled, a course of plasmapheresis may be of benefit in the preoperative period (22). The steroid-dependent patient will require perioperative coverage.

Anxiolytic, sedative, and opioid premedications are rarely given to patients who may have little respiratory reserve. If the patient has primarily ocular symptoms, a small dose of benzodiazepine is acceptable.

Response to Anesthetic Drugs

Nondepolarizing Neuromuscular Blockers

Neuromuscular blocking drugs act by interrupting neuromuscular transmission at the level of the nicotinic acetylcholine receptors at the motor end plate. Their mode of action can be classified as antagonist (nondepolarizing) or agonist (depolarizing), both producing blockade (23). The myasthenic patient is typically sensitive to nondepolarizing neuromuscular blockers. The use of a small dose for priming or defasciculation is not appropriate, because it may result in loss of airway protection or in respiratory distress. Sensitivity to nondepolarizing agents has been described in patients with minimal disease (i.e., ocular symptoms only) (24), in those in apparent remission (25), or those with subclinical undiagnosed myasthenia (26).

Long-acting muscle relaxants such as d-tubocurarine, pancuronium, pipecuronium, and doxacurium, are best avoided in these patients. Intermediate and short-acting nondepolarizing agents can be used with careful monitoring of neuromuscular transmission, preferably with electromyogram (EMG) or mechanomyogram

(MMG), which measure the evoked electrical or mechanical responses following electrical stimulation of a peripheral motor nerve. Stimuli can be delivered singly (0.1 Hz or one every 10 seconds; 1 Hz or one per second), or in trains-of-four (TOF) stimuli (2 Hz) at 10-second intervals. In the absence of a neuromuscular block, a control response is obtained. This control "twitch" is designated Tc. In the absence of a neuromuscular block, all responses should be of equal magnitude. Thus, with TOF stimulation, the control, first, second, third and fourth responses are equal (Tc=T1=T2=T3=T4). In the presence of a nondepolarizing block, Tc>T1 and T4<T3<T2<T1. The ratio of T4 /T1 is called the fade ratio and is used to assess the extent of a nondepolarizing block. In the presence of a depolarizing or phase I block (due to succinylcholine) Tc>T1 but T1=T4, i.e., there is no fade with this type of block. Sometimes a phase I block changes in nature and takes on the characteristics of a nondepolarizing block (i.e., fade develops). The latter block is called a phase II block.

In myasthenic patients, the ED_{95} for vecuronium ranges from 40% (17 μg/kg vs. 24 μg/kg) (27) to 55% (20 μg/kg vs. 36 μg/kg) (28) of that in normal controls. There are wide variations in responses among myasthenics. Elimination of vecuronium is not altered.

Wide variability in requirements was also noted for atracurium (29). The ED_{95} was 58% (0.14 mg/kg vs. 0.24 mg/kg) of the value for normal patients (30). Myasthenic patients are similarly sensitive to cisatracurium, as evidenced by a more rapid onset and more marked neuromuscular block compared with control patients (31).

Increased sensitivity to mivacurium has also been reported (32). Recovery was prolonged (recovery index 25–75% for T1 of 20.5 minutes vs. 11.9 minutes) in a patient receiving pyridostigmine (33). Pyridostigmine inhibits the metabolism of mivacurium and therefore increases recovery times when mivacurium is administered. It should therefore be used with caution in patients receiving pyridostigmine on the morning of surgery.

Depolarizing Neuromuscular Blocker (Succinylcholine)

Patients with MG show resistance to depolarizing agents (34–36). It is probable that the requirements are increased due to the loss of receptors, because these agents create neuromuscular block by agonist action. The ED_{95} of succinylcholine in MG patients is 2.6 times that in non-myasthenic patients (0.8 mg/kg vs. 0.3 mg/kg) (34). The dose of succinylcholine used for rapid airway control in normal patients, 1.5 mg/kg, is approximately five times the ED_{95} in MG. A dose of 1.5–2.0 mg/kg should be adequate for most myasthenics, for rapid sequence intubation (34). A case report of a myasthenic patient in complete remission showed a normal sensitivity to succinylcholine (37). Myasthenic patients are more likely than normal patients to develop a phase II block, particularly with repeated doses of succinylcholine (38). Cholinesterase depletion due to plasmapheresis (39) or inhibition caused by pyridostigmine given preoperatively may affect the metabolism of succinylcholine (40) and mivacurium (32), resulting in prolonged blockade.

Potent Inhaled Anesthetic Agents

Inhaled anesthetics may cause muscle relaxation in normal patients (41). This effect may be profound. Isoflurane depresses T1 and increases train-of-four fade in the myasthenic patient (42). It produces twice as much twitch height depression as equipotent concentrations of halothane (43). There may be some variability in the response among myasthenics (41, 44). Train-of-four responses are also decreased to varying degrees in myasthenic patients receiving enflurane (45, 46).

Sevoflurane at 2.5% — slightly greater than 1 MAC (minimum alveolar concentration) — depresses (EMG) responses, with T1/Tc at 47% and T4/T1 at 57% (47). A recent report found sevoflurane was suitable as a sole anesthetic for a myasthenic undergoing sternal split thymectomy, implying that sevoflurane alone provided adequate muscle relaxation (48). Sevoflurane appears to depress neuromuscular transmission to the same degree as isoflurane, although in one myasthenic patient the sensitivity was much greater (>85% T1 suppression) (49). TOF stimulation in most patients anesthetized with halothane revealed measured decrements in evoked responses (50).

Although to date no work has been reported on the effects of desflurane in myasthenics, in normal patients the requirements for muscle relaxants are decreased in the presence of desflurane (51, 52). It is likely that in myasthenic patients desflurane will have the same effect as the other potent, inhaled, volatile anesthetic agents discussed above.

Intravenous Anesthetic Agents

Anesthetic management using barbiturates and propofol for myasthenic patients without untoward effects have been described (53, 54). Propofol has the theoretic advantages of short duration of action without effect on neuromuscular transmission.

Opioid analgesics in therapeutic concentrations do not appear to depress neuromuscular transmission in myasthenic muscle (55, 56). However, central respiratory depression may be a problem with opioids. The introduction of short-acting opioids makes these drugs more titratable in the myasthenic. Remifentanil's short elimination half-life (9.5 minutes) (57) makes the drug appealing. To date, there are no reports of its use in MG. There are reports of uneventful anesthesia using etomidate (58), althesin (58) and ketamine in myasthenic patients (59).

Interactions with Other Drugs

Many commonly used drugs affect neuromuscular transmission to a small degree. In normal patients, this is usually of no clinical significance. In the myasthenic patient, upon emergence from anesthesia and surgery, the interactions of these drugs with residual anesthetic effect and the disease state of MG may be more significant.

The most commonly used drugs known to depress neuromuscular transmission are the aminoglycoside antibiotics and the polymyxins (60–62). Beta adrenergic blockers, regardless of their mode of administration, have been shown to exacerbate MG (63, 64).

Corticosteroids, although used in the treatment of MG, may also exacerbate MG (62). Corticosteroids have not been shown to affect the dose-response to succinylcholine, but they have been shown to decrease the dose requirements for nondepolarizing relaxants in myasthenics (65). Procainamide was reported to cause weakness in a myasthenic patient (66). Phenytoin has caused clinical weakness in a myasthenic patient (67); however, it has been used without clinical side effects for seizure disorders in patients with MG (68).

Regional Anesthesia

Potentiation of neuromuscular blocking drugs by local anesthetics has been reported (69, 70). These agents decrease the sensitivity of the postjunctional membrane to acetylcholine (71). This theoretically could cause weakness in myasthenics if blood levels are high enough. Ester anesthetics, which are metabolized by cholinesterase, may present particular problems in patients taking anticholinesterases. Regional and local anesthesia should be performed using reduced doses of amide (rather than ester) local anesthetics to avoid high blood levels. Traditionally, blockade of the innervation of intercostal muscles is avoided to minimize the risk of respiratory muscle weakness. Recently, however, the safe and successful use of thoracic epidural blockade with bupivacaine for intraoperative anesthesia and postoperative analgesia for transsternal thymectomy has been reported (72, 73). Spinal anesthesia has the advantage of reduced drug dosage, whereas epidural techniques facilitate easier control of blockade level and may obviate the need for opioids in postoperative pain management.

Anesthesia Management

The safe use of general anesthesia requires attention to monitoring the patient and understanding the variable responses that the myasthenic may have to many drugs. The EMG and the mechanomyograph are the preferred methods for monitoring neuromuscular transmission. They record control values to compare with those elicited throughout surgery and postoperatively. Recently, submaximal train-of-four stimulation in awake patients has been advocated (74). Similarly, the presence of fade ($T4/T1 < 0.9$) in the preanesthetic period predicts decreased atracurium requirements in patients with MG (75). This technique, along with preoperative pulmonary function testing (17), may be useful in determining preoperative baseline function.

Several general anesthetic techniques have been proposed, although none has been proven to be superior to the others. Some prefer to avoid muscle relaxants altogether and use potent inhaled agents both for facilitating tracheal intubation and providing relaxation for surgery. These agents allow neuromuscular transmission to recover, with rapid elimination of these agents at the end of surgery. In theory, desflurane and sevoflurane may offer some advantages, due to their low blood solubility. Sevoflurane is probably superior to desflurane, due to its lower incidence of excitatory airway reflexes during inhalational induction. Others titrate small doses (10–25% of the ED_{95}) of intermediate-acting relaxants to the evoked MMG or EMG for both intubation and surgical relaxation, if required. The decision as to whether to reverse residual neuromuscular blockade at the end of surgery is controversial. Some argue that the presence of anticholinesterases and antimuscarinics will confuse efforts to differentiate weakness due to inadequate neuromuscular transmission from cholinergic crisis in the recovery room. They prefer spontaneous recovery and extubation when the patient has demonstrated adequate parameters for extubation (i.e., head-lift, tongue protrusion).

Total intravenous anesthesia (TIVA) for the management of myasthenics has been reported (53). In the authors' experience, hemodynamic instability in older patients makes this approach difficult, whereas younger patients usually tolerate it without difficulty. The use of remifentanil as part of TIVA may alleviate some of the hemodynamic instability.

When possible, many clinicians prefer to utilize regional or local anesthetic techniques. Regional techniques may reduce or eliminate the need for muscle relaxants in abdominal surgery. Epidural techniques offer the advantage of postoperative pain control with minimal or no opioid use.

Postoperative Considerations

There have been several attempts to predict the need for postoperative ventilation (17, 76, 77). Based on the preoperative condition of the patient, the surgical procedure, and the residual anesthetic effects, a carefully planned extubation may be carried out in most patients. Adequate postoperative pain control, pulmonary toilet, and the avoidance of drugs that interfere with neuromuscular transmission will facilitate tracheal extubation. All patients with MG should be closely monitored postoperatively in the postanesthesia care unit or the surgical intensive care unit, where respiratory support can be immediately reinstituted. Weakness after surgery presents a special problem in MG patients. The differential diagnosis includes myasthenic crisis, residual effects of anesthetic drugs, nonanesthetic drugs interfering with neuromuscular transmission and cholinergic crisis.

Cholinergic Crisis

Cholinergic crisis results from an excess of acetylcholine at the nicotinic and muscarinic receptors. It usually results from administration of excess anticholinesterase drugs. Nicotinic overstimulation results in involuntary twitching, fasciculations, and weakness (sometimes leading to respiratory arrest). The weakness results from an inability to coordinate muscle contraction and relaxation. When the muscarinic effects are obvious, the diagnosis is easily made. Antimuscarinics and respiratory support are indicated. When acetylcholinesterase inhibition in conjunction with antimuscarinics has been used to reverse residual neuromuscular blockade, weakness and fasciculations may predominate in the absence of muscarinic symptoms. To differentiate this from myasthenic crisis, an edrophonium (Tensilon®) test may be administered. Also, in a myasthenic crisis, the pupils will be dilated. In the absence of muscarinic symptoms, simply allowing the patient to recover clinically, without elaborate testing, while maintaining mechanical respiratory support, constitutes a safe and practical approach. For these reasons, many clinicians prefer to avoid the use of muscle relaxants, or if they do so, to allow the neuromuscular block to recover spontaneously, avoiding the use of anticholinesterase in the immediate postoperative period.

Conclusions

Myasthenia gravis is a disease with many implications for the safe administration of anesthesia. The potential for respiratory compromise in these patients requires the anesthesiologist to be familiar with the underlying disease state, as well as the interaction of anesthetic and nonanesthetic drugs with MG. Thymectomy is a surgical procedure commonly undergone by patients with MG.

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Advances in Labor Analgesia

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Abstract

Approximately two-thirds of all women in the United States receive analgesia for labor and delivery. The ideal labor analgesic technique would confer complete pain relief without side effects to either the mother or the neonate. The analgesic technique would not cause any lower extremity motor blockade nor interfere with the progress or course of labor and would be sufficiently flexible to produce anesthesia for forceps or cesarean deliveries. Modern obstetric analgesia techniques and medications come close to achieving these goals. The following article will review current labor analgesia techniques and medications used during labor and delivery.

Key Words: Advances, analgesia, epidural, combined spinal-epidural, local anesthetics.

Introduction

ANALGESIA FOR LABOR AND DELIVERY is now safer than ever. Anesthesia-related maternal mortality has decreased from 4.3 per million live births during 1979 – 1981 to 1.7 per million live births during 1988 – 1990. The increased use of regional anesthesia for the parturient is partially responsible for this decrease in mortality (1). The pain of labor is mediated by nerves that enter the neuraxis at the 10th, 11th, and 12th thoracic spinal segments and at the 1st lumbar spinal segment. These nerves can be blocked by administering medication into either the epidural or the subarachnoid space. Our goal is to provide labor analgesia, not anesthesia. Analgesia is the absence of sensation to pain whereas anesthesia is the absence of all sensation.

The epidural space is located between the ligamentum flavum and the dura mater and can be located by applying pressure to a fluid- or air-filled syringe connected to a needle as it is advanced through the back and ligamentum flavum. While the needle is in the ligamentum flavum, there is almost complete resistance to injection through the needle. As the needle tip passes into the epidural space, the resistance to injection disappears and the air or saline is easily injected. A catheter through which medication can be administered is threaded into the epidural space. The medication utilized is 10 – 15 mL of bupivacaine 0.125 – 0.25% with fentanyl 50 – 100 micrograms. The exact dose of medication is based on the severity of labor pain at the time of catheter placement. The subarachnoid space is found by advancing a needle through the dura mater and visualizing subarachnoid fluid in the hub of the needle. Fentanyl 25 micrograms with 1 mL of bupivacaine 0.25% is administered. The medication lasts only approximately 1.5 – 2 hours. A catheter is not threaded into the subarachnoid space. Subarachnoid analgesia is usually utilized in conjunction with epidural analgesia.

Safety is the first and foremost goal of obstetrical anesthesia. For labor analgesia, a secondary goal is to minimize or eliminate maternal lower extremity muscle weakness associated with epidural and subarachnoid local anesthetics. Patients with less motor block are more satisfied with their anesthetic experience (2). Also, decreasing motor blockade may improve obstetric outcome. Although controversial, motor blockade related to labor epidural analgesia has been implicated as a cause of forceps deliveries and cesarean delivery (3). Minimizing the motor blockade may attenuate or eliminate these effects (4) and may allow women to ambulate during labor. Single isomer local anesthetics such as levo-bupivacaine and ropivacaine have been developed that may be safer and produce less motor blockade than their stereoisomer counterparts. The purpose of this article is to review analgesic techniques and medications that are currently used to provide labor analgesia.

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Epidural analgesia has been the most popular technique for the relief of labor pain, because of its efficacy and safety. Women can obtain almost complete relief from the pain of labor. Because a catheter can be threaded into the epidural space, dilute solutions of local anesthetic can be injected during the earlier stages of labor to achieve analgesia. As labor progresses, a more concentrated solution of local anesthetic can be administered, or an adjunct, such as an opioid, can be added. Additionally, an epidural catheter can be utilized to maintain a low dermatomal level of analgesia for labor (T10–L1) and, if needed, the dermatomal level can be raised to T4 for cesarean delivery.

Local anesthetic are most commonly utilized for labor epidural analgesia. Opioids are often added to the local anesthetic to decrease the motor block, but they do not confer adequate analgesia for labor pain when used alone unless large doses are used (5). Continuous infusions of epidural local anesthetic combined with an opioid are frequently employed during labor. Continuous infusions provide a more stable level of analgesia than intermittent bolus techniques. This technique results in better analgesia for the mother and a decreased workload for the anesthesiologist (6). Without the frequent bolus injections, there may be less risk of maternal hypotension (7, 8). Interestingly, maternal satisfaction does not appear to be greater when continuous infusions are utilized compared with intermittent boluses (9). Most women who receive continuous infusions tend to receive greater doses of bupivacaine than those who received intermittent injections (8, 9). The continuous infusion solutions currently used usually contain 0.04–0.125% of a local anesthetic (bupivacaine or ropivacaine) plus an opioid (fentanyl or sufentanil) (10, 11).

Some anesthesiologists use patient-controlled epidural analgesia (PCEA). This technique allows the patient to self-medicate, thereby controlling her own analgesia. Because there are few well-controlled studies regarding PCEA, the optimal dosing regimens have not been determined. Compared with continuous infusion or intermittent bolus techniques, PCEA is associated with fewer anesthesiologist interventions and less motor block (7, 12). Less anesthesia also decreases the frequency of maternal hypotension (7). The total dose of local anesthetic used is less with PCEA (13, 14), and maternal satisfaction is greater than when standard epidural analgesia techniques are used (15). Unfortunately, not all studies have documented all these advantages and therefore few hospitals offer this technique (16, 17). A commonly used PCEA regimen is bupivacaine 0.0625% with fentanyl 2 µg/mL with the following PCEA settings; basal rate of 10 mL/hr, bolus dose of 5 mL, 10 minute lockout, and a 30 mL/hr maximum limit. This author is not aware of any complications to the parturient with PCEA use. But theoretical risks include those that have been seen in the general surgical patient including high dermatomal level or overdose from excessive self-administration, from a helpful family member, or secondary to a catheter that has migrated into the subarachnoid space.

The safety of epidural opioids has been well documented. Despite decreased neonatal neurobehavioral scores shortly after delivery (18), epidural fentanyl has not been linked to any long-term (four years) developmental effects (19). The clinical relevance of lower neurobehavioral scores around the time of delivery is unknown, but some have suggested that epidural fentanyl may impact on the ability of the neonate to breast feed (20). This concern is not based on scientific evidence. Indeed, Halpern et al. (21) did not find any difference in breast feeding success among neonates whose mothers received epidural fentanyl versus those who did not (21). Respiratory depression in the neonate is also of little concern with epidural fentanyl. Respiratory parameters of neonates whose mothers received epidural fentanyl (up to 400 g) are similar to those whose mothers did not receive any fentanyl (22).

There are a number of problems with labor epidural analgesia that have prompted the use of alternative techniques. First, the time from epidural catheter placement until the patient is comfortable is variable, but depending on the local anesthetic used, can take up to 30 minutes. Other disadvantages of labor epidural analgesia include maternal hypotension, inadequate analgesia (15–20% of cases) (23) and motor block, even with the very dilute local anesthetic solutions (11).

Subarachnoid opioids offer rapid, intense analgesia with minimal changes in blood pressure (24) or motor function (25). The opioid is usually administered as part of a combined spinal epidural (CSE) technique. After locating the epidural space in the usual manner, a long small-gauge spinal needle with a pencil-point design is inserted through the epidural needle into the subarachnoid space. A subarachnoid opioid, either alone or in combination with local anesthetic, is injected. The spinal needle is removed and an epidural catheter threaded for future use. Analgesia begins within 3 – 5 minutes and lasts 1 – 1.5 hours. When the analgesia wears off the epidural catheter is utilized for the remainder of labor. Or, a continuous epidural infusion of dilute local anesthetic/opioid solution is started immediately after securing the epidural catheter. Starting the epidural infusion immediately, versus waiting for pain to recur, prolongs the spinal medication by approximately 60 minutes with minimal side effects and is highly recommended (26). It would be tempting to thread a catheter into the subarachnoid space to enable administration of repeated doses of opioid into this space. Unfortunately, there may be a risk of cauda equina syndrome when placing subarachnoid catheters, especially microcatheters (27). A study is currently underway to evaluate the safety of subarachnoid microcatheters (28).

Subarachnoid administration of fentanyl 25 micrograms (0.5 mL) or sufentanil 5 micrograms (0.1 mL) are the opioids most commonly utilized with the CSE technique. Differences between the two drugs are subtle and choice of one over the other is based on personal preference. However, the cost of sufentanil is $7.50 for a 2 mL ampule whereas a 2 mL ampule of fentanyl costs $0.21. The balance of the opioid from the vial is generally saved for later use in the same patient or discarded if not used. Palmer et al. (29) found that the ED50 of subarachnoid fentanyl is 14 µg and that the duration of action increased to 89 minutes as the dose increased to 25 µg. Above 25 µg the duration of action was not prolonged. Herman et al. (30) found that the ED50 for subarachnoid sufentanil was 2.6 µg and the ED95 was 8.9 µg. Adding 1 mL of bupivacaine 0.25% to either fentanyl or sufentanil does not hasten the onset of block, but prolongs the duration by about 20 min for fentanyl (31) and 30 minutes for sufentanil (32). Side effects of adding bupivacaine are minimal and may protect the patient from developing pruritus (33). Whether this added duration is worthwhile is based on personal preference. At Mount Sinai we commonly use fentanyl 25 µg with 1 mL of bupivacaine 0.25% for the subarachnoid dose.

The CSE technique has several advantages. The primary one is the rapid (3 – 5 min) onset of analgesia. Additionally, Collis et al. (2) found less motor block and greater patient satisfaction in parturients receiving the CSE technique versus the "standard" epidural technique of bupivacaine 0.25%. The greater satisfaction was related to the faster onset of action and less motor block.

There are some concerns about the CSE technique, most of which are only theoretical. There is no increased risk of subarachnoid catheter migration of the epidural catheter (34) and metallic particles are not produced as a result of passing one needle through another (35). Norris et al. (36) found that the incidence of postdural puncture headache is not increased with the CSE technique. An increase in end-tidal carbon dioxide has been reported in women who received subarachnoid sufentanil (37), but the risk of clinically significant respiratory depression is low (38). Also, the risk of hypotension with the CSE technique is not greater than with standard epidural regimens. Grant et al. (25) found minimal changes in maternal blood pressure in nonlaboring term parturients following 25 µg of subarachnoid fentanyl. This was true in women who received prehydration with 1,200 mL crystalloid solution and those who did not receive any prehydration. The most common side effect of subarachnoid opioids is pruritus, with a reported incidence as high as 95% (33, 39), which is easily treated with either an antihistamine or naloxone.

It is possible that the epidural catheter may not actually be in the epidural space after the CSE technique is performed, and this may not be detected until the analgesia from the subarachnoid opioid has dissipated (1 – 2 hours). If, during this time period, the woman requires an emergent cesarean delivery, the catheter may fail and the patient may require a general anesthetic. Norris et al. (40) found that the risk of failed epidural catheters was lower in women who received CSE analgesia than those who received epidural analgesia. However, it is prudent not to use the CSE technique in a woman who is a poor risk for general anesthesia, e.g., one with a bad airway or obesity, so that in these patients it is important to assure that an epidural catheter can and will function satisfactorily.

Clarke et al. (41), in 1994, reported fetal bradycardia associated with uterine hypertonus after subarachnoid opioid injection. One proposed theory for increased uterine tone is related to the rapid decrease in maternal catecholamines associated with the onset of pain relief. With the decrease in circulating beta adrenergic agonists, there is enhanced alpha activity that leads to uterine contractions (42). Three retrospective studies did not find any difference in the incidence of fetal heart rate abnormalities with CSE analgesia versus epidural analgesia (43–45). A large retrospective review found no difference in the incidence of emergency cesarean delivery in 1,217 women who received CSE analgesia versus 1,140 who did not receive neuraxial analgesia (46). If hypertonus occurs, treatment should include subcutaneous terbutaline or intravenous nitroglycerin (47).

There have been several recent prospective studies evaluating the effects of the CSE technique on the incidence of cesarean delivery. Nageotte et al. (48) randomized women to three groups: group 1 received CSE with sufentanil 10 μg, group 2 received the same technique and medication as those in group 1 but were encouraged to ambulate, and group 3 received epidural analgesia. They did not find any difference in the need for cesarean delivery between the three groups of patients. Gambling et al. (49) compared women who received CSE analgesia versus those who received intravenous meperidine during labor, and they too did not find any difference in the incidence of cesarean delivery between the 2 groups.

The term "walking epidural" has become popular especially in the lay community. It refers to any epidural or spinal technique that allows ambulation. Some studies have suggested that ambulating or being in the upright position is associated with a shorter first stage of labor, less pain in early labor, and decreased analgesia requirements (50, 51). These findings have not been confirmed in prospective, randomized studies. Indeed, two recent well-designed prospective and randomized studies have not been able to document any medical benefit of ambulating, either in terms of duration of labor or mode of delivery (48, 52).

In many centers, few patients want to ambulate. Most want to rest or sleep once they have pain relief. However, even if patients do not want to ambulate, using a technique that produces minimal motor blockade will improve patient satisfaction (2). Either epidural analgesia using dilute local anesthetic/opioid solutions or a CSE technique can be used to achieve this goal. Several precautions should be taken before allowing a parturient to walk during epidural or CSE analgesia. Maternal blood pressure and fetal heart rate should be monitored for 30–60 minutes after induction (49) and intermittently thereafter since small doses of subarachnoid and epidural local anesthetics can produce some motor deficits (2, 10). Motor function should be assessed by having the parturient perform a modified deep knee bend or stepping up and down on a stool. The patient must have an escort at all times, and fetal heart rate and maternal blood pressure should be reassessed at least every 30 minutes.

Local Anesthetics

Bupivacaine gained popularity for use in obstetrics because of its long duration of action and relative motor sparing as compared to other local anesthetics. It is also compatible with other medications commonly used during labor epidural analgesia, especially opioids. However, bupivacaine has a narrow margin of safety (dose that causes analgesia is close to the dose that causes cardiovascular symptoms). In 1979, Albright reported several cases of cardiovascular collapse, most of which were fatal, in the parturient who received inadvertent intravascular injections of bupivacaine (53). Because of these reports, the United States Food and Drug Administration (FDA) banned the use of epidural bupivacaine 0.75% in the parturient. This has led to the search for a safer local anesthetic for the parturient.

Local anesthetics produce their effects on nerve conduction by blocking the passage of sodium ions through the sodium channels in the plasma membrane. Amide local anesthetics exist as one of two enantiomers, levo or S(–) and dextro or R(+). In general, the levo form is more potent as an anesthetic, but is less cardiotoxic than the dextro form. The reduced cardiotoxicity is related to a lower affinity of the levo isomer for the sodium channels in the plasma membrane of cardiac cells (54). Bupivacaine is commercially produced as a racemic mixture of its two enantiomers, levo-bupivacaine and dextro-bupivacaine. The levo-isomer of ropivacaine, as well as levo-bupivacaine, are now available for use.

Initial studies suggested that ropivacaine may be less cardiotoxic and produce less motor block than bupivacaine, thus making it an ideal agent for labor analgesia. Feldman et al. (55) found, in the canine model, that the lethal dose of intravenous ropivacaine was greater than that of bupivacaine. Although there are no cardiotoxicity studies of ropivacaine in humans, Scott et al. (56) found, in human volunteers, that a larger intravenous dose of this drug was tolerated prior to the onset of neurologic symptoms than was the case for intravenous bupivacaine. In the surgical patient, Brockway et al.

(57) found that less motor block developed in the patients who received ropivacaine than in those who received bupivacaine. In the parturient, however, both McCrae et al. (58) and Stienstra et al. (59) were unable to detect less motor block when ropivacaine was utilized for labor analgesia as compared to bupivacaine. In these studies (55, 56, 58, 59), the same concentrations of ropivacaine and bupivacaine were utilized. Subsequently, two separate investigators (60, 61) demonstrated that epidural ropivacaine is significantly less potent than epidural bupivacaine by a factor of 0.57. The author is not aware of any study that has compared the potency of ropivacaine and levo-bupivacaine. Thus, the decrease in motor block or toxicity found in the previously studied ropivacaine groups may have been related to the lesser potency of ropivacaine.

Levo-bupivacaine is equipotent to racemic bupivacaine (62) and has been found to be less cardiotoxic than bupivacaine in human volunteers (63). Two studies have been completed in parturients comparing bupivacaine with levo-bupivacaine. Both studies found that the quality and onset of analgesia and lower extremity motor block were similar for the two drugs (64, 65).

The challenge facing obstetric anesthesiologists is to define the role of these new local anesthetics for the parturient. Although using a drug less toxic than bupivacaine is important, the risk of cardiac problems from modern day doses and concentrations of bupivacaine (0.625 – 1.25%) for labor is close to zero. Furthermore, even before the introduction of ropivacaine and levo-bupivacaine, modifications in clinical practice including the use and test-dosing of multi-orifice epidural catheters, the use of dilute concentrations of local anesthetic, and the fractionation of the total dose of local anesthetic has made epidural anesthesia very safe. Indeed, the estimated maternal mortality rate from regional anesthesia decreased from 8.6 per million regional anesthetics in 1979 – 1984 to 1.9 per million in 1985 – 1990 (1). Another important consideration is cost. At The Mount Sinai Hospital, a 30 mL vial of bupivacaine costs approximately $1.00, whereas a similar volume and concentration of levo-bupivacaine and ropivacaine costs approximately $6.00. Despite this cost differential, the author believes, in view of the information currently available, that these latter two drugs may be preferred for use in women with limited cardiac reserve, e.g., those with mitral stenosis, severe preeclampsia, or pulmonary hypertension. The author also prefers using levo-bupivacaine or ropivacaine for women undergoing cesarean delivery where the otherwise larger amounts (both volumes and concentrations) of alternative local anesthetic agents may increase the likelihood of an adverse reaction.

In summary, techniques and drugs available to the obstetric anesthesiologist are vastly superior to what existed previously. The future of obstetric anesthesia lies in refining these techniques and drugs to make obstetric anesthesia even safer and more effective.

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Central Neuraxial Analgesia in Cardiac Surgery

Octavio Falcucci, M.D.

Abstract

An ideal anesthetic for cardiac surgery should provide intraoperative cardiovascular stability and a stable and pain-free recovery. High-dose narcotics, whether given as an initial bolus or by the continuous infusion method, certainly have brought current practice closer to this ideal. Central neuraxial analgesia is an alternative to high-dose narcotics, but its use has long been an issue of debate and concern in cardiac surgery. The need for full heparinization for cardiopulmonary bypass has curtailed the use of central neuraxial blocks. Until fairly recently, very few centers dared to attempt this kind of effective analgesia in cardiac surgery. However, during the last few years more and more reports have been published on the efficacy and safety of this type of analgesia when appropriate precautions are taken. The objective of this report is to examine some of these issues.

Key Words: Central neuraxial analgesia, cardiac surgery.

The Need for Pain Relief

In the postoperative period, it is necessary to ensure adequate respiration by clearing bronchial secretions. There is also a paramount need for the relief of pain, which may be a primary cause of postoperative complications (1, 2).

Impairment of lung function, particularly oxygenation of the blood, is a common and potentially serious complication after cardiac surgery. It has been shown to persist for as long as a week after the operation. It presents frequently with a reduced arterial oxygen tension and hemoglobin oxygen saturation when breathing room air (3–5). Some proposed mechanisms are leukocyte activation (6), effects of anesthesia and muscle paralysis (7, 8), sternotomy (9), pleurotomy (10), extracorporeal circulation (ECC) (11, 12), accumulation of extravascular lung fluid (13) due to alterations of the alveolar-capillary membrane (14, 15), lung collapse during ECC (16), atelectasis (17), phrenic nerve paralysis secondary to topical cooling of the heart (17), altered mechanics of the rib cage (9, 18), retention of airway secretions consequent to insufficient cough due to pain (19), and postoperative hypoventilation. Atelectasis is the most important cause of postoperative morbidity and occurs in nearly all patients undergoing thoracotomy (20). Large densities in dependent lung regions were seen in most patients by computed tomography (21) on the first day after cardiac surgery. Postoperative respiratory abnormalities found after abdominal or thoracic surgery have a restrictive pattern, with decreased vital capacity and functional residual capacity (22). The desired objective of limiting the extent of decreased pulmonary function would be a worthy goal if effective pain relief could be achieved without respiratory depression.

Since it has also been shown that postoperative myocardial ischemia has a high predictive value for myocardial infarction, providing effective analgesia might reduce this risk (23).

Effectiveness of Intrathecal Morphine

The discovery of opioid receptors in the substantia gelatinosa of the spinal cord has fostered new options for the effective management of postoperative pain (24).

Intrathecal morphine (ITM) provides very powerful postoperative analgesia of impressive duration with little disturbance of consciousness (25). A unique advantage of ITM is that morphine can be injected at a lumbar site and then diffuse into the thoracic portions of the spinal cord to provide pain relief (11). There is ample evidence that ITM produces good analgesia (22, 26, 27), and is superior to IV morphine for patients undergoing coronary artery

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bypass grafting (CABG) (28, 29). In Fig. 1, the results of three different studies are compared. One group of patients received ITM in addition to the standard narcotic-based anesthetic whereas the control group received only a narcotic-based anesthetic. The data from the ITM group reveals that the cumulative amount of morphine administered during the first 24 hours after surgery was significantly less than that required by the control group.

There is little apparent intraoperative hemodynamic difference between CABG patients receiving ITM 0.5 mg and those receiving a standard narcotic anesthetic (30). ITM does not suppress hyperdynamic responses per se, unless supplemented with a local anesthetic. Kowalewski et al. (31) showed that the combination of ITM and bupivacaine limited hyperdynamic responses to sternotomy and surgery by achieving a cardiac sympathectomy.

In the postoperative period, patients who received ITM had significantly less need for vasodilators. Fig. 2 compares the percentage of patients who received vasodilator therapy during the first 24 hours postoperatively and those who did not. Vanstrum et al. (30) reported a 35% reduction in the use of sodium nitroprusside. Patients who received ITM or thoracic epidural analgesia (see below) had less need for vasodilators. This suggests that patients who received ITM were more hemodynamically stable during this postoperative period than those patients who had received ITM. The need for fewer infusions of vasoactive drugs decreases the chance of a medication error and reflects a generally more benign course.

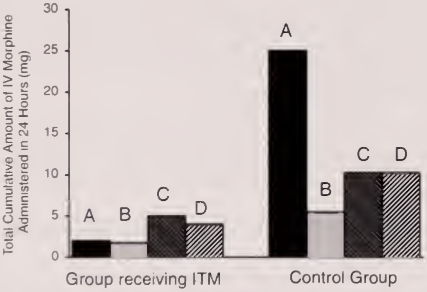

Fig. 1. The total cumulative dose of morphine (mg) administered intravenously during a 24-hour period as reported by three groups of investigators. Data depicted by the bars labeled A are those reported by Shroff and Bishop (34). An ITM dose of morphine of 0.01 mg/kg morphine was administered and the difference is significant ($p<0.01$). Data illustrated by the bars labeled B are those reported by Vanstrum, Bjornson and Ilko (30). An ITM dose of morphine of 0.5 mg morphine was administered and the difference is significant ($p<0.05$). Data shown by the bars labeled C and D, are those reported by Fitzpatrick and Moriarty (29). Those patients whose data are included in the bars labeled C received an ITM dose of morphine of 1 mg ($p<0.01$), while those whose data are included in the bars labeled D received 2 mg ($p<0.01$).

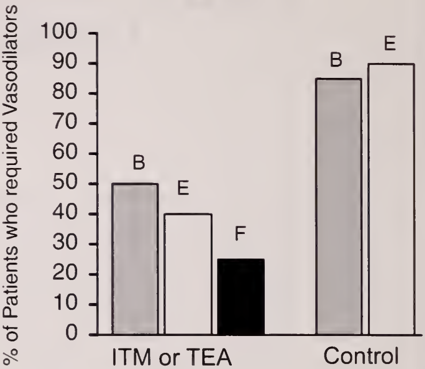

Fig. 2. The percentage of patients who required vasodilators. Data illustrated by the bars labeled B are those reported by Vanstrum, Bjornson and Ilko, see Fig. 1. (30) ($p<0.05$). Data shown by the bars labeled E are those reported by Liem et al. (37). In these patients, TEA was administered together with general anesthesia. The TEA infusion included bupivicaine 0.125% and sufentanil 1:1,000,000, and was administered at 0.05 mL/cm body length /hr adjusted to a VAS pain score less than 6. Their control group did not receive TEA. The difference is significant ($p<0.05$). Data depicted by the bar labeled F, were reported by Taylor et al. (32). These patients received an ITM dose of morphine of 0.03 mg/kg. A control group was not included.

Respiratory Depression

The merits of ITM have been offset by the increased incidence of late respiratory depression. Since CABG patients generally spend the first 24 hours postoperatively in intensive care, adequate monitoring and skilled staff can deal with this problem safely and rapidly should it be necessary to do so.

The rostral spread of morphine in the subarachnoid space to the cisterns and then to the pons is thought to be responsible for the diminished respiratory drive (24). The reported incidence of respiratory depression is 0.36 – 1.9% (24, 32). This rostral spread may also cause drowsiness (33). In one study, the time to extubation was not significantly altered by ITM use (30), and, in some reports, it was improved (29, 34). Peak expiratory flow rates were also improved (29). Arterial blood gas result trends were favorable, but these did not reach statistical significance (30). There is evidence to suggest that the incidence of side effects, particularly respiratory depression, is related to the dose of ITM. Samii et al. (35) and Gjessing and Tomlin (25) observed that respiratory depression after ITM is dose-related. Consequently, the current tendency is to use lower doses. Early reports of ITM involved doses as high as 20 mg (35), but now the reported ranges are generally 5 – 30 µg/kg for patients undergoing heart surgery. If respiratory depression occurs, intravenous naloxone is the treatment of choice, since the cautious administration of naloxone does not alter the quality of analgesia. This phenomenon has been observed by several investigators (29, 36). This persistence of analgesia and the improvement in ventilation probably result from lower concentrations of morphine near the respiratory centers than in the vicinity of the spinal cord, and may be associated with the local analgesic action of ITM.

Thoracic Epidural Analgesia

Thoracic epidural analgesia (TEA) is another option for the management of postoperative and intraoperative pain. TEA offers several benefits: it reduces perioperative stress, the incidence of myocardial ischemia and postoperative pain, and it is also likely that it reduces complications (25). “Fast-tracking” is enhanced, awakening and extubation occur earlier, breathing is facilitated, and patients can be mobilized sooner (37).

The use of TEA for intraoperative and postoperative analgesia, when compared with IV analgesia, provides significant improvement of perioperative pulmonary function (1). This improvement is attributed to better pain relief and to the increased postoperative alertness of patients receiving TEA (2). It also produces less depression of the ventilatory response to carbon dioxide and less atelectasis than IV morphine in non-cardiac thoracic surgery (38, 39). Liem et al. (37) found that P_aO_2 was significantly higher in a group of patients treated with TEA following CABG.

Joachimsson et al. (40) described how, in patients with TEA that were efficiently rewarmed, extubation of the trachea could be performed within the first 2 postoperative hours after CABG without increasing metabolic and ventilatory requirements.

There are several indications that TEA improves the myocardial oxygen supply-demand balance. A lower incidence of myocardial ischemia was observed in TEA patients compared with general anesthesia (GA) patients after CABG (37). Kock et al. (41) observed less ST segment depression in the electrocardiogram during exercise in patients with TEA. In another study, it was shown that regional cardiac sympathetic blockade with TEA that included the T1 – T4 segments, increased the diameter of stenotic epicardial coronary arteries significantly ($p<0.01$), without causing dilation of coronary arterioles (42). In dogs, cardiac sympathetic blockade reduced myocardial ischemia, improved ischemic zone perfusion and reduced infarct size (43). TEA can be used to provide pain relief in patients with acute myocardial infarction or unstable angina pectoris, with acceptable hemodynamics (44, 45). Both blockade of nociceptive afferent nerves and relief of myocardial ischemia may contribute to the relief of angina (45). It also improves left ventricular global and regional wall motion abnormalities and ST segmental changes (41).

Thoracic Epidural Analgesia versus Intrathecal Morphine: A Comparison

TEA and ITM reduce postoperative pain, levels of stress, serum cortisol levels, and the need for antihypertensive drugs after CABG. When ITM was supplemented with local anesthetics, or TEA was added to GA, hemodynamic stability was improved and the stress response to sternotomy was attenuated (31, 46). ITM has some advantages over TEA: simplicity, reliability, low dose requirements, and the absence of the need to place a catheter in the epidural space, but has the disadvantage of possible respiratory depression.

The unique pharmacokinetic aspects of the epidural space complicate the epidural administration of opioids. For example, systemic absorption and sequestration into epidural fat will influence the amount of drug that reaches receptors in the spinal cord by diffusion across the dura mater. To offset the effects of systemic absorption and fat sequestration, the epidural dose of opioids is about 10 – 16 times greater than that required for subarachnoid injection (47).

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Several studies confirm that the duration and quality of analgesia after intrathecal opioids equal or exceed those produced by epidural administration of morphine. In these same studies, evidence of depression of ventilation occurs after epidural morphine (5 mg) but not after intrathecal morphine (250 μg), despite the fact that mean duration of analgesia (28 hours for post-caesarian section pain) produced by the lower dose of morphine exceeds that which followed the epidural injection (22, 47–50). These facts suggest that TEA, to be effective in cardiac surgery, needs to be based on local anesthetic infusion and not on epidural morphine. Therefore, the placement of the catheter must be in the high thoracic region, a procedure that is technically more challenging than a lumbar intrathecal injection. If local anesthetics are used, TEA, unlike ITM, provides sympathetic blockade and coronary vasodilatation as noted previously. TEA also allows for continuous analgesia beyond 24 hours, in contrast to the single injection ITM technique.

Neuraxial Hematoma and Heparinization

The use of ITM or TEA in patients undergoing cardiac surgery is well established. Since these patients are heparinized intraoperatively, its use remains controversial. Lumbar subarachnoid puncture or thoracic epidural placement followed by heparinization may result in a neuraxial hematoma, with the potential for permanent neurologic damage (51). This fear has so far restricted the use of ITM and TEA in cardiac surgery, but the risk may not be as great as previously believed (30, 40, 46, 52). The true risk may never be established precisely due to the rarity of the event (51).

Several factors are known to increase the risk of hematoma development after lumbar puncture. These include the skill with which the procedure was performed, the number of attempts made, whether the tap was traumatic, the size of the needle used, and concomitant coagulopathy or anticoagulant therapy.

Owens et al. (51) described a patient who was heparinized 135 minutes after a technically difficult diagnostic lumbar puncture. Sixteen hours later, the patient became paraplegic. In a literature review, Owens found 33 cases of neuraxial hematoma reported since 1911, 79% involving patients with evidence of hemostatic abnormality from anticoagulation, thrombocytopenia, coagulopathy, or antiplatelet therapy (71).

Rao and El-Etr (53), and Matthews and Abrams (54) demonstrated that a decision to postpone surgery after a difficult or traumatic (bloody) tap, and subsequent care in performing the spinal tap, avoided the occurrence of subarachnoid hematoma. In their respective studies, they investigated 847 patients who had continuous spinal anesthesia and 3164 patients who had continuous epidural anesthesia that was initiated prior to heparinization for vascular surgery. A large 17-gauge Tuohy needle was used to place the catheters in both studies.

The size of the needle was not reported by Owens et al. (51). The use of 25- and 27-gauge needles is relatively recent. One could speculate that the already rare complications reviewed by Owens et al. might be further reduced by the current use of smaller gauge needles in combination with the cautious technique described by Rao and El-Etr.

In another review covering the years 1906 through 1994, Vandermeulen et al. (55) found 61 reported cases of neuraxial hematoma after central nervous block. Of these, 42 patients had impaired coagulation. Despite this, epidural techniques were used in combination with heparin anticoagulation in four large series, for a total of 5776 cases, without any report of permanent neurologic sequelae (53, 56–58). It was also used in conjunction with cardiac surgery in several smaller (30, 40, 46, 52, 59, 60) and one large (61) study, without complications. In this larger study, Sanchez and Nygård (61) examined outcomes in 558 CABG patients who received TEA and found no occurrence of epidural hematoma. Stenseth et al. (62), and Joachimsson et al. (40), have described the use of high thoracic epidural catheter placement during CABG. They found no neurological sequelae when the catheter was inserted 20–24 hours prior to heparinization, and when there were no coagulation disorders at the time of catheter insertion and removal. Taylor et al. (32) reported the use of ITM in more than 10,000 cardiac surgery patients during a 20-year interval in whom there was no evidence of a spinal hematoma.

Conclusions

The utilization of TEA or ITM for cardiac surgical patients provides benefits in perioperative pain control and lung function, and it presumably decreases morbidity secondary to respiratory complications. These techniques are associated with improved hemodynamics and myocardial oxygenation, early awakening and extubation. The potential risk of a neuraxial hematoma is of concern, and its real incidence, probably lower than previously thought, will require further study.

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Current Trends in Pediatric Anesthesia

Ingrid Hollinger, M.D.

Abstract

New trends in pediatric anesthesia for ambulatory surgery will be described. Preoperative preparation as well as care of pediatric patients requiring sedation outside of the operating room are emphasized.

Key Words: Pediatric anesthesia, sedation.

Pediatric Anesthesia for Ambulatory Surgery

Most elective pediatric surgical procedures are performed on an outpatient basis. The ideal anesthesia for pediatric ambulatory surgery promotes rapid recovery, provides adequate postoperative analgesia, and avoids postoperative nausea and vomiting.

While total intravenous anesthesia (TIVA) has become popular for adult outpatient anesthesia, it is not frequently utilized with pediatric patients, because of the difficulty in establishing intravenous access in children who are awake. However, the discomfort of intravenous line placement may be minimized by the use of EMLA cream (eutectic mixture of 2.5% lidocaine and 2.5% prilocaine) applied 45 minutes prior to venipuncture. EMLA cream also reduces the pain of other procedures involving needlesticks, such as lumbar punctures or the repair of minor lacerations. Because of their synergistic effect, a combination of a sedative/hypnotic agent with an opioid provides a smooth anesthetic and reduces the individual agent's total dose. Propofol is ideally suited for TIVA, because of its rapid onset and termination of effect. Because of their larger volume of distribution and faster clearance, pediatric patients require higher bolus and infusion doses/body weight compared to adults (1). Propofol reduces the incidence of nausea and vomiting, particular after emetogenic procedures such as otological or ophthalmological surgery. In addition, emergence delirium is uncommon after propofol (2).

The new, ultra-short-acting narcotic, remifentanil, has been used in pediatric anesthesia (3). The blood-brain equilibration is prompt, accounting for its rapid onset. Since it is rapidly hydrolyzed by plasma esterases to inactive metabolites, its duration of action is not influenced by hepatic or renal clearance. Its context-sensitive half-time, the time required for a 50% decrease in plasma concentration following an infusion regimen designed to maintain a constant plasma concentration for a specific period of time, is approximately 3 minutes irrespective of dosing and duration of infusion (4).

Since the primary narcotic effect of remifentanil ends so quickly, other modalities of postoperative pain relief must be utilized. Postoperative analgesia can be provided by a number of drugs, including acetaminophen, a potent non-steroidal anti-inflammatory agent such as ketorolac, a longer-acting narcotic such as fentanyl or morphine-sulfate, or supplemental local and regional nerve blocks. Acetaminophen is effective for postoperative pain relief, but it must be given in adequate doses (e.g., 40 mg/kg rectally) (5). Nerve blocks are particularly useful after orthopedic and surgical procedures below the umbilicus or on an extremity. Caudal and epidural techniques, as well as inguinal, penile, axillary, and femoral nerve blocks, have been used successfully in pediatric patients. Preemptive local and regional anesthesia leads to smoother emergence; the incidence of nausea and vomiting is decreased, since narcotics are avoided (6).

Because of its ease of administration, inhalation anesthesia is still the technique most widely practiced for pediatric patients. The

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minimum alveolar concentration (MAC) of the anesthetic that prevents movement as a response to skin incision in 50% of patients increases after the first month of life, peaks at approximately 6 months and progressively declines throughout childhood until adulthood. Depth of anesthesia can easily be controlled by changing inspired concentration and manipulating minute-ventilation and/or total fresh gas flow. Inhalation anesthetics are cleared rapidly; this rapid recovery may lead to emergence delirium, particularly if pain relief is inadequate (7, 8). Sevoflurane is the most widely used new volatile anesthetic for children. Because of its low blood-gas solubility as well as the high minute-ventilation to functional residual capacity (FRC) ratio in children, sevoflurane has a rapid onset of action. Sevoflurane has a low incidence of airway irritability and minimal cardiovascular side effects. In contrast, desflurane leads to an unacceptable incidence of airway complications when used to induce anesthesia.

NPO Guidelines and Preoperative Laboratory Assessment

One of the most unpleasant aspects of preoperative preparation for parents and children has been the required blood tests and the directives regarding feeding and fluid intake. Changes in these have recently been introduced.

Measurement of hematocrit is particularly important for infants less than 6 months old, since there is a high incidence of unrecognized anemia, which may be a risk factor for perioperative apnea and cardiac arrest (9). Patients over the age of 6 months with no pre-existing medical disease (such as sickle-cell anemia, diabetes, renal or hepatic failure) require no preoperative laboratory studies (10).

Reducing the time of preoperative fasting diminishes the extent of dehydration and possibility of hypotension on induction of anesthesia (11). This must be balanced against the risk of aspiration of gastric contents in the perioperative period. However, numerous studies have failed to document an increased risk of perioperative aspiration in healthy patients when fasting guidelines were relaxed (12, 13). For this reason, the American Society of Anesthesiologists (ASA) adopted new guidelines on perioperative fasting in October 1998 (14). These guidelines allow for the intake of clear liquids until 2 hours before the planned procedure, breast-milk until 4 hours before the planned procedure, and infant formula, milk or a light meal until 6 hours before the procedure. With these guidelines, there is less stress on parents to keep a toddler happy during the preoperative period.

Sedation outside the OR

Minor surgical procedures performed outside the operating room, invasive diagnostic or therapeutic procedures, and non-invasive diagnostic studies requiring the patient to remain immobile for extended periods of time require sedation for a majority of pediatric patients. Although anesthesiologists are providing this service more frequently, there are not enough anesthesiologists for all patients. Many insurance carriers are unwilling to reimburse physicians for these services. To safeguard pediatric patients, the American Academy of Pediatrics first issued guidelines for the elective use of conscious sedation, deep sedation, and general anesthesia in 1985; these guidelines were updated in 1992 (15). In 1996, the American Society of Anesthesiologists issued "Practice Guidelines for Sedation and Analgesia by Non-anesthesiologists" (16). The American College of Radiology (17) and the American College of Emergency Room Physicians (18) have also issued guidelines for sedation, as have various other subspecialty groups like critical care, cardiology, gastroenterology and endoscopy. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has appointed the anesthesia department as the watchdog in every institution to assure that sedation is performed appropriately and safely (19). The JCAHO defines conscious sedation as "a state that allows patients to tolerate unpleasant procedures while maintaining adequate cardiorespiratory function and the ability to respond purposefully to verbal commands." Unfortunately, in pediatric patients, conscious sedation is rarely achievable. Patients must be sedated and monitored by appropriately trained individuals, and back-up systems must be available to quickly manage any complication. The JCAHO standards dictate that standards that are applicable to the administration of general anesthesia are also applicable to children undergoing sedation (19).

The institutional performance-improvement system approves physicians and sedation protocols and monitors compliance and complications (20). In a prospective review of 1140 cases of pediatric sedation by non-anesthesiologists, the sedation failure rate was 13.2% and oxygen desaturation occurred in 5.5% of the cases. Higher ASA classifications and age less than 1 year old were significant risk factors for complications (20). Another prospective case study of 1180 cases reported a 2.3% complication rate; 50% of the reported adverse events were oxygen desaturation (21). Despite the institution of sedation-analgesia protocols in all hospitals as mandated by JCAHO, there is wide variability in the training and expertise of the practitioners performing these procedures. In a review of 17,500 computed tomography (CT) scans of the head, performed in pediatric emergency rooms and requiring conscious sedation, only 73% of the practitioners had training in this technique, and 10% were unaware of the national guidelines (22). In order to provide a higher standard of care, dedicated teams in many institutions have been established to provide sedation to children. A retrospective review of one of these services demonstrated a 12% complication rate, most frequently oxygen desaturation, apnea, airway obstruction, and mild hypotension (23). This alarmingly high frequency of complications occurred because the sedation protocol allowed non-anesthesiologists to use drugs that had been restricted to use only by anesthesiologists. In many of these situations, general anesthesia was administered by non-anesthesiologists. For this reason, the report by Lowrie et al. (23) was severely criticized by Krane (24), Yaster and Maxwell (25), and Means et al. of the Section on Anesthesiology of the American Academy of Pediatrics (26). Lowrie et al. replied to these criticisms (27).

Sedation protocols must also be reviewed by the pharmacy and therapeutics (P&T) committee at each institution to assure appropriate dosing for pediatric patients. For non-painful procedures, chloral hydrate is still the most widely used sedative in pediatrics. Sedation failure may be avoided by the use of adequate induction doses (50–100 mg/kg orally). Pentobarbital (2 mg/kg IV to a maximal dose of 5–6 mg/kg) is commonly used for diagnostic radiology when patients are monitored by a nurse. Midazolam administered via the oral, rectal, intravenous, or intranasal route is frequently used in combination with a narcotic such as morphine sulfate, fentanyl or meperidine, or ketamine in sub-anesthetic doses. The advantage of a benzodiazepine-narcotic combination is the availability of specific antidotes in case of overdose. Intravenous general anesthetics have a high potential for respiratory complications, and therefore should generally be used only by anesthesiologists. However, these agents may be safely used in intubated and ventilated patients by non-anesthesiologists. For painful procedures, the addition of local anesthesia may allow reduction in the dose of sedatives. Adequate pain relief in the initial stages of repeated painful diagnostics (e.g., lumbar puncture) may prevent later escalation of sedative requirements (28). EMLA can be extremely useful for these indications and in the emergency room.

Patient safety remains the most important mandate for anesthesiology. New developments in pediatric anesthesia, which hold the promise of enhancing patient and parent comfort, always need to be evaluated to identify and prevent any increased risk. Adherence to national sedation guidelines, institutional protocols approved by the anesthesia department and P&T committee, along with the appropriate monitoring capabilities allows pediatric sedation to be performed safely and effectively by non-anesthesiologists in areas outside the operating rooms. Oversight by the institutional performance improvement and quality assurance committees acts as an additional safeguard. The accepted techniques have all gone through extensive clinical trial and/or scientific scrutiny. The risk of anesthesia is the lowest it has been since the introduction of general anesthesia into clinical practice anesthesia in 1842; however, this safety record can be maintained only if a physician-anesthesiologist is involved in the care of the patients requiring anesthesia (29).

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Complications of Spinal Anesthesia

HATIM HYDERALLY, M.D.

Abstract

Serious neurological complications after spinal anesthesia are rare, but do occur. The most common are postdural puncture headache and hypotension. Hypotension after spinal anesthesia is a physiological consequence of sympathetic blockade. The diagnoses and management of these sequelae are discussed.

Key Words: Regional anesthesia, complications, spinal anesthesia, postdural puncture headache, transient radicular irritation, cauda equina syndrome, neurologic deficits.

PROFESSOR AUGUST BIER performed the first surgical operation using spinal anesthesia at the Royal Surgical Hospital of the University of Kiel, Germany on August 16, 1898, heralding the advent of major regional anesthesia using neuraxial blockade (1). In 1927, spinal anesthesia was performed by Gaston Labat at The Mount Sinai Hospital (2). Since then, of course, it has been well incorporated into the practice of anesthesiology.

The complications of spinal anesthesia may be categorized as:

- spinal – postdural puncture headache
- cardiovascular
- neurologic

Postdural Puncture Headache

Postdural puncture headache is the most common complication of spinal anesthesia. It occurs most frequently in young adults including obstetric patients, with an incidence rate of 14%, compared to 7% in individuals older than 70 years.

The use of smaller needles with pencil-point tips has markedly reduced the incidence of postdural puncture headaches. These intense headaches occur when cerebrospinal fluid (CSF) escapes through the dural puncture site, resulting in intracranial tension on meningeal vessels and nerves. Prompt treatment is essential and consists of bed rest, adequate hydration (orally or intravenously), and the use of analgesics. If conservative therapy fails, an epidural blood patch with 10 – 15 mL of autologous blood injected at the site of the "meningeal" tear may be necessary to minimize further leakage of CSF. This modality is very effective in relieving symptoms despite the fears of infection and neurological sequelae (3).

Cardiovascular Complications

The incidence of hypotension following spinal anesthesia is 10 – 40%. The hypotension is related to the extent of sympathetic blockade, which is responsible for a decrease in systemic arteriolar and venous tone. Cardiac output may fall as a result of the decreased venous return (4).

Significant hypotension should be treated with appropriate administration of intravenous fluids and judicious use of vasoactive drugs such as ephedrine or phenylephrine.

Cardiac arrest has been reported in healthy patients during administration of a spinal anesthetic (4). The cardiac arrest occurs suddenly, often preceded by severe bradycardia in an otherwise hemodynamically stable patient. In these cases, hypotension or hypoxemia is not a precipitating cause. It is postulated that the etiology of the bradycardia and asystole might be a reflex mechanism such as the Bezold-Jarisch reflex (4).

Neurologic Complications

The incidence of severe neurologic deficits following spinal anesthesia is low. In a prospective study of 40,640 cases of spinal anesthesia, the authors reported an incidence rate of serious neurological deficits of 0.5 per 10,000 (confidence intervals 0.2 – 1.1 per 10,000) (5). When they do occur, they are of great concern to both the patient and the practitioner. Despite the low incidence, many pa-

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tients reject spinal anesthesia because they fear this complication.

The most benign neurologic complication is aseptic meningitis. This syndrome usually presents within 24 hours of spinal anesthesia and is characterized by fever, nuchal rigidity and photophobia. Microscopic examination of CSF is characterized by polymorphonuclear leukocytosis; bacterial CSF cultures are negative. Aseptic meningitis requires only symptomatic treatment and usually resolves within a few days.

Cauda equina syndrome presents after regression of the neuraxial blockade. This syndrome may be permanent, or it may regress slowly over weeks or months (6). It is characterized by a sensory deficit in the perineal area, urinary and fecal incontinence, and varying degrees of motor deficit in the lower extremities.

The most serious neurologic complication is adhesive arachnoiditis. This reaction usually occurs several weeks or even months after spinal anesthesia. The syndrome is characterized by a gradual progression of sensory deficits and motor weakness in the lower limbs. There is a proliferative reaction of the meninges and vasoconstriction of the spinal cord vasculature.

Spinal cord ischemia and infarction may occur after prolonged periods of arterial hypotension (6). The use of epinephrine in anesthetic solutions may reduce blood flow to the spinal cord (6). Traumatic injury to the spinal cord and nerve roots is a rare cause of neurologic deficits. In the past, syringes and ampules of local anesthetic medications were sterilized by immersion in phenolic disinfectant solutions. This chemical contamination has been implicated as a cause of neurologic complications following spinal anesthesia.

Transient neurologic symptoms consisting of severe radicular back pain after neuraxial blockade regression were reported in 1960 following spinal anesthesia with 5% lidocaine. There were no sensory or motor deficits, and the symptoms resolved spontaneously within a few days. The etiology of this radicular pain was unclear. The incidence was greater with the use of lidocaine compared with bupivacaine and was more common in patients having surgery with the hips or knees in the flexed position (7).

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Anesthetic Considerations for Endovascular Aortic Repair

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Abstract

Endovascular aortic repair is a new alternative to conventional surgical techniques. A variety of devices available for endovascular aortic repair are discussed and the outcomes after repair are reviewed. Anesthetic considerations during endovascular repair are dictated by the device being used, as well as the site of device deployment. Requirements for the optimization of hemodynamic states during proximal graft deployment are described, as well as the available options for induction of ventricular asystole. Since arterial rupture is always a risk when using this procedure, appropriate facilities must be present for resuscitation. Patients undergoing repair of thoracic aortic pathology may be candidates for perioperative transesophageal echocardiographic monitoring. Since a subgroup of these patients may be at risk for postoperative paraplegia, aggressive spinal cord protection should be considered. Patients with large aneurysms may be at risk for "post-implantation syndrome," which is characterized by hyperpyrexia, hypotension, and coagulopathy.

Key Words: Endovascular surgery, anesthesia, aortic aneurysms, aortic repair, transesophageal echocardiography, adenosine, cardiac asystole, ventricular fibrillation, paraplegia.

Endovascular aortic repair is a new alternative to conventional surgical repair of aortic pathology (1). This technique of aortic repair was first suggested by Dotter in 1969 (2) and was used in clinical applications after the work of Parodi et al. in 1990 (3). Since this early work, this technology has been applied to the treatment of peripheral artery aneurysms (4, 5), diffuse aorto-iliac occlusive disease (6), and traumatic arterial injuries (7). The main advantage of using endovascular grafts is that this technique is less invasive than conventional arterial reconstructions. It is the only technique which allows these grafts to be inserted from remote access sites. Avoiding laparotomy or thoracotomy eliminates the need to directly dissect the aorta, which can be further complicated by local acute trauma or scarring from previous aortic surgery.

The advantages of this technique include: (a) it is a less invasive procedure, which allows the use of local, regional, or minimal general anesthesia; (b) the period of aortic occlusion during graft placement is insignificant; (c) there is less hemodynamic and metabolic stress to the patient; (d) the patient can ambulate and be discharged earlier; and possibly (e) the overall cost may be less.

During endovascular aortic repair, a remote arterial site such as the femoral artery is exposed and isolated. A large endovascular stent-graft delivery system is introduced into the femoral artery and is advanced under fluoroscopic guidance to the diseased aortic segment. When the final position of the stent-graft is reached, the device is deployed within the aorta. After deployment, the stent-graft excludes the lesion from central aortic flow (Fig. 1).

Surgical Considerations and Outcome

There are three types of endovascular devices commonly used for repair of infrarenal abdominal aortic aneurysms (AAA). The aorto-uni-femoral endograft (Fig. 2) consists of a single, tapered, tubular endograft that originates in the infrarenal aorta and is either surgically attached in an end-to-end fashion to the femoral artery or is attached to the iliac artery. The con-

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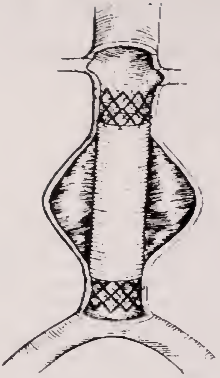

Fig. 1. Schematic of endovascular aortic repair. The endograft bridges the diseased aortic segment, excluding it from central aortic flow.

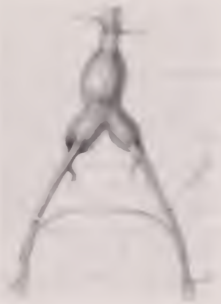

Fig. 2. The aorto-uni-femoral endograft. (See text for description.) The stent-graft excludes the infrarenal aortic aneurysm as it carries blood from the infrarenal aorta to the right femoral artery. A femoral artery to femoral artery shunt is constrructed to provide blood flow to the left leg. An occlusion device is inserted into the left iliac artery to prevent retrograde flow into the aneurysm.

tralateral iliac artery is permanently occluded to prevent retrograde flow from the iliac artery into the aneurysm sac. A femoral-to-femoral arterial conduit is constructed, to provide contralateral lower extremity blood flow. The advantage of using this technique is that it is a relatively simple graft construction and is less dependent on iliac artery anatomy than other devices. The major disadvantage is the need for surgical reconstruction.

A second type of device is the single-piece, bifurcated aortic endograft, which consists of a singular device that begins in the infrarenal aorta and straddles the aortic bifurcation (Fig. 3). Because of this single-piece design, the graft construction and delivery are complex, thereby requiring graft dimensions to be determined at the time of manufacture. The single-piece design allows for less chance of leakage or stenosis than do devices of a modular-type design.

Finally, endovascular grafts with a modular design consist of separate limbs that are constructed *in situ* in the aorta (Fig. 4). These are the most common types of devices presently being evaluated for use in the infrarenal aortic segment. Because of this modular design, the individual grafts and the delivery system are simpler. Customized graft-component selection may be available at the time of procedure, resulting in more dynamic sizing. The major disadvantage of the modular design is the greater potential for leakage, disconnection, or stenosis at the graft overlay zones.

Not all patients are candidates for endovascular repair. The proximal aneurysm neck (i.e., "landing zone") must be at least 15 mm in length, and the aneurysm diameter should be no larger than the largest endograft available. The distal attachment site must be non-aneurysmal and of sufficient length to accommodate the graft. Finally, there must be at least one large,

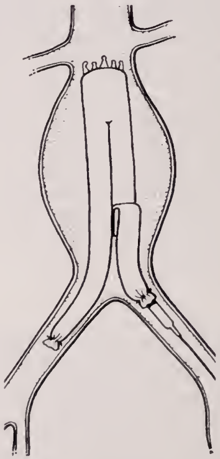

Fig. 3. Single-piece, bifurcated aortic endograft. The proximal aspect of the graft (top) lies distal to (below) the renal arteries and extends as a unit into both iliac arteries.

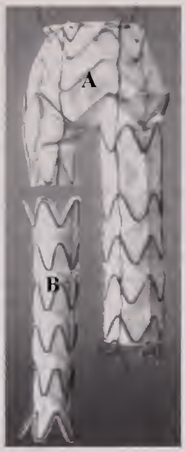

Fig. 4. Two components of a modular aortic endograft are shown. The larger component **(A)** on the right is attached below the renal artery and extends into one iliac artery. The smaller component **(B)** is inserted into the larger one and extends into the contralateral iliac artery, excluding the infrarenal aortic aneurysm from central aortic flow.

straight iliac artery that can be used as a conduit for the delivery system. After these considerations, approximately 40–60% of patients presenting for endovascular repair are candidates for treatment.

Cuypers et al. reported an initial technical success rate after one month (defined as uneventful vascular access, deployment, and patency of the endovascular graft without obstruction or endoleak) of 78% in their series of 64 patients undergoing infrarenal AAA repair (8). After six months, many small endoleaks resolved, which resulted in a clinical success rate of 83%. Their reported continued success during their follow-up period was 77%. Age and American Society of Anesthesiologists (ASA) status were significant risk factors in increased mortality; age and operator experience were significant risk factors in complications, and operator experience was a significant risk factor in the occurrence of endoleaks. In another series, Blum et al. prospectively treated 154 patients undergoing infrarenal AAA repair, with an endovascular device (9). They reported complete exclusion of the aortic pathology from central aortic flow in 86% of the patients. Of these 154 patients, 3 patients required conversion to open repair, 3 experienced major complications, and 13 experienced minor complications.

Dake et al. reported six-month, one-year, and two-year survival rates of 86%, 81%, and 73% respectively after endovascular thoracic aortic aneurysm (TAA) repair (10). The predictors of death included patients who were not surgical candidates, those who needed cardiopulmonary bypass (CPB) when they underwent combined ascending aortic and arch surgery with endovascular TAA repair, those with large aneurysm or large aneurysm neck diameter, and older patients. The major complications of the procedure were early death (9%), and neurological (10%) and pulmonary (12%) problems. The 9% mortality rate did not differ much from the reported 11% mortality incidence of open repair; however, it should be noted that 16% of these patients were operated on an emergency basis, and 60% of these patients were not candidates for open repair. In this context, this mortality rate is not unreasonable. The high incidence of stroke may have been caused by catheter or sheath manipulations in the aortic arch and ascending aorta, excessive anticoagulation, or possibly surgical manipulation of the carotid or subclavian arteries.

Use of endovascular techniques may be a treatment option for aortic dissections as well. The endograft is positioned at the site of the intimal tear. By inhibiting the continued flow of blood into the false lumen, end-organ ischemia and infarction are prevented and future aneurysm formation is retarded by facilitating thrombus formation in the false lumen. Nienaber et al. reported technical success in 12 patients with type B aortic dissections; there was no morbidity or mortality during the perioperative and follow-up periods (11). Dake et al. treated 4 patients with type A dissections and 15 with type B aortic dissections, with an endovascular repair of intimal tears of the descending thoracic aorta (12). Repair was technically successful in all patients; complete false lumen thrombosis was achieved in 15 patients (79%) and partial thrombosis was achieved in 4 (21%). There was an early mortality rate of 16%, but there were no instances of death or rupture during the subsequent follow-up interval, which averaged 13 months.

Because of iliac artery or aortic anatomy, the operator may be unable to pass the sheath or delivery device through diseased arteries. The possibility of iatrogenic arterial rupture always exists with intra-arterial manipulations, so facilities for resuscitation must be available. Endoleaks may develop at the attachment sites, resulting in continued leakage from central aortic flow into the diseased aortic segment. These endoleaks may be a result of intimal plaque distortion, severe neck angulation, aneurysm neck calcification, stent migration, or inappropriate endograft size. Renal injury, either segmental or total, may occur as a complication of endovascular aortic repair. The possible etiologies of renal injury are renal artery occlusion by the endograft or renal artery dissection, embolism, and contrast-induced toxicity. Although there may be interference with hypogastric flow, complications have not been reported.

Techniques for Proximal Graft Deployment

Distal migration of the device occurring during proximal endograft deployment may result in inadequate exclusion of the aneurysm sack, with resultant endoleak. One technique used for the insertion and deployment of the endovascular aortic device employs large balloon angioplasty catheters to expand and secure the proximal stent attachment system of the endovascular graft to the underlying vessel wall (Fig. 5). These balloons have a large cross-sectional area, predisposing them to distal aortic migration as a result of the forces exerted by forward aortic blood flow. Device malposition secondary to inadvertent migration may result either in occlusion of major arterial branches or incomplete aneurysm exclusion. The use of induced hypotension during device deployment may reduce the magnitude of migration; however, significant endovascular stent-graft movement may occur nonetheless because of continued aortic blood flow. The risk of malposition may be further decreased by ventricular asystole, which can be achieved either by pharmacological induction of complete heart block and ventricular arrest with high-dose adenosine (13) or, alternatively, by induced ventricular fibrillation (14). Ventricular fibrillation is a highly invasive technique reserved for patients who require prolonged periods of controlled ventricular quiescence, while adenosine, in high doses, appears to be a safe method to induce short periods of temporary asystole.

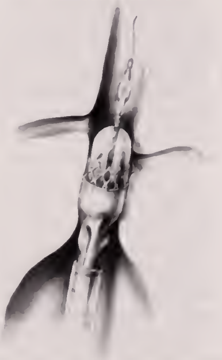

Fig. 5. Proximal aortic endograft deployment by large balloon angioplasty catheter. During deployment, the large profile of this device may result in distal device migration and in incomplete aneurysm exclusion.

Induced Hypotension

The newer endografts are either thermally or mechanically activated during proximal graft deployment. Since angioplasty balloons are not used to deploy the endograft, the graft need not display the large profiles associated with first-generation devices that required an angioplasty balloon. Because of this lower profile, minimal induced hypotension (using fast-acting venous or arterial vasodilators), or no interventions are usually adequate for proximal stent deployment.

Adenosine-Induced Asystole

In order to increase the accuracy of device positioning, Dorros et al. proposed the technique of administering high-dose adenosine to induce temporary high degree AV block and asystole during device deployment (15). Adenosine is an endogenous nucleoside analog that exerts negative dromotropic and chronotropic effects, both at the sinoatrial and atrioventricular nodes. Its major therapeutic use is to terminate supraventricular tachycardias. Adenosine's half-life is very short ($t^1/2$ less than 10 seconds) due to its rapid enzymatic breakdown and reuptake into erythrocytes and vascular endothelial cells. The asystole produced with adenosine is not reduced by atropine. Adverse effects of adenosine are usually very transient and include flushing, chest pain, throat tightness, blurred vision, dizziness, numbness, and dyspnea. Although Dorros et al. reported the safety of this technique in a limited number of patients, we reported similar outcomes in approximately 100 patients (13).

From January 1997 to March 1999, 98 patients received adenosine to induce asystole for endovascular stent-graft placement. Patients selected for this trial had infrarenal aneurysms (≥ 5 cm in diameter) and significant medical comorbidities, as determined by standard criteria (16, 17), placing these patients at a presumed increased risk of a major complication or of death during conventional AAA repair.

In the operating room, the radial artery was cannulated. In addition, a catheter was inserted into the right internal jugular vein and advanced into the pulmonary artery to measure the pulmonary artery pressure. Temporary external transthoracic pacing and defibrillation pads were placed for the possible management of either prolonged AV block or atrial arrhythmias after the adenosine administration. A temporary transvenous ventricular pacing lead was inserted as an alternative to the external transthoracic pacing pads. Regional anesthesia was preferentially used in conjunction with sedation during the induced asystolic period. Local anesthesia with sedation (2 patients) or general anesthesia (2 patients) was induced when regional anesthesia was technically difficult, inadequate, or contraindicated.

Immediately prior to stent-graft deployment, patients were sedated with etomidate (0.1 –0.2 mg/kg) or propofol (1 – 2 mg/kg). This sedation avoided the uncomfortable sensations associated with adenosine-induced asystole, as well as the discomfort of the aortic distention during angioplasty balloon inflation. All patients who had permanent indwelling pacemakers had their devices reprogrammed in order to prevent pacemaker capture during induced asystole (9 patients). Patients who were not pacemaker dependent (6 patients) had their pacemakers programmed off prior to the surgical procedure; patients who were pacemaker dependent either had their pacemakers programmed off just prior to adenosine-induced asystole (2 patients) or alternatively, had the pacemaker temporarily suppressed via external chest wall stimulation (1 patient), as previously described by our group (18). After final confirmation of device placement by angiography, adenosine 24 mg was rapidly administered via a central venous catheter which was usually inserted via the sideport introducer of the pulmonary artery catheter (PAC). Patients who did not have a sustained period of asystole following a bolus of adenosine were then given escalating doses of adenosine (48 mg, 60 mg, and 90 mg) until asystole was achieved. Deployment balloon inflation attached the proximal endograft to the aortic wall. After successful device deployment, the temporary pacemaker was activated if the duration of asystole exceeded 15 – 20 seconds.

The adenosine dose range was 24 – 90 mg, with a median value of 24 mg. No patients developed bronchospasm or required treatment for worsening obstructive pulmonary disease during or after adenosine administration. No patient required the initiation of inotropic support after induced asystole. Two patients had transient episodes of myocardial ischemia (diagnosed by ST segment depression), each of which resolved without sequela within 30 seconds after baseline rhythm return. Two patients developed atrial fibrillation after adenosine administration that responded to synchronized direct current cardioversion using the external transthoracic defibrillation pads. One patient developed a transient left bundle branch block of less than 10 seconds duration that did not adversely affect hemodynamics. Four patients required activation of his or her temporary pacemaker to treat a prolonged period of asystolic response to adenosine. In each of these cases, the duration of temporary pacing was less than 30 seconds, after which time the patient returned to his or her baseline rhythm.

In this series, we have demonstrated the safety of high-dose adenosine. Although there was significant interpatient variability, doses may be titrated to provide the necessary minimum of approximately ten seconds of asystole without adverse reactions. By decreasing the propulsive effects of aortic blood flow, induced asystole provided aortic conditions that appeared to decrease the incidence of endovascular stent-graft malpositioning. Although two patients had detectable endovascular stent-graft migration, the etiology was likely secondary to unanticipated premature ventricular contractions. No patients had exacerbations of pre-existing obstructive or reactive pulmonary disease and no patients required prolonged inotropic support as a result of adenosine administration. Although 6 (6.2%) of the 98 patients required either cardioversion for atrial fibrillation or brief activation of a temporary pacemaker, these effects were easily treated and no adverse outcomes were associated with these interventions. Sedation during adenosine administration appeared to ameliorate many of these sensations.

Ventricular Fibrillation during Proximal Stent Deployment

There are a very few cases of endovascular aortic repair that require prolonged periods for proximal stent deployment. High doses of adenosine have been used to induce temporary asystole or high degree AV nodal blockade during the device deployment (13, 15). Unfortunately its duration of action is unpredictable, premature ventricular contractions may occur and return of normal sinus rhythm may return prior to complete device deployment (our previous unpublished experience with abdominal aortic endograft-stent repairs). Early return of normal sinus rhythm after adenosine administration may result in inadequate time for device deployment and balloon deflation. Concern is greatest with intrathoracic deployment of endovascular stent-grafts when temporary complete aortic occlusion during device deployment can exert the greatest propulsive force on the incompletely deployed aortic endograft.

An alternative technique to induce temporary asystole for endograft deployment employs induced ventricular fibrillation (14). Ventricular fibrillation may be induced either by rapid ramp pacing or by applying alternating current to the endocardial surfacing, using an AC fibrillator via pacing electrodes (19). Ventricular fibrillation is a highly invasive technique, which has been reserved for patients who require prolonged periods of controlled ventricular quiescence. To date, we have used and reported this technique of induced ventricular fibrillation during the care of four patients over five procedures (14).

In order to use the technique of induced ventricular fibrillation, Zoll multifunction external electrodes (Burlington, MA) were applied under the left breast and posteriorly to the left of midline at the level of the scapula. Radial artery catheterization was performed and general anesthesia was induced with propofol, fentanyl, and pancuronium. An Edwards Swan-Ganz thermodilution Paceport Catheter (Irvine, CA) was placed via the right jugular vein and a ventricular lead (Edwards Flex-Tip Transluminal V-Pacing Probe) was properly positioned. Fluoroscopy confirmed that external defibrillator pad placement would not interfere with subsequent aortic arch imaging. The ventricular leads were connected via standard temporary transvenous pacemaker cables to an alternating current transformer (Medtronics, Minneapolis, MN). A 10-second trial of ventricular fibrillation was induced by activation of the A/C transformer, and the patients were successfully defibrillated by discontinuation of the alternating current and administration of one 200-joule (J) shock via the external pads. Baseline hemodynamics rapidly returned to baseline levels. After successful induction of ventricular fibrillation and defibrillation, the patients were actively cooled, using a cooling blanket, to 34°C during surgical preparation.

After confirmation of precise stent placement, the position of the ventricular lead was reconfirmed by the presence of 1:1 capture during ventricular pacing. The ventricular lead was reattached to the alternating current source and the generator was activated. Ventricular fibrillation was instituted and was confirmed by a flat intraarterial pressure tracing. Over the next 90 seconds, the angioplasty balloon was inflated, and the stent was deployed and preliminarily confirmed to cross and exclude the pseudoaneurysm by both fluoroscopy and transesophageal echocardiography (TEE). After deflation of the angioplasty balloon, the alternating current was discontinued, and the patients were defibrillated using 200 J of current. Most patients had post-resuscitation hypertension that was easily controlled with a single dose of sodium nitroprusside 40 µg, while one patient had post-resuscitation hypotension that responded to a single dose of epinephrine 8 µg.

Because the period required for complete device deployment was unknown, intentional mild hypothermia was induced in order to provide both cerebral and myocardial protection. Mild hypothermia has in many experimental preparations conferred significant cerebral protection (20). Hypothermia may also provide some degree of myocardial protection during ventricular fibrillation (21). These beneficial effects of hypothermia were felt to outweigh the possible deleterious effects of possible increased perioperative morbid cardiac events or wound infections (22, 23).

Transesophageal Echocardiography during Thoracic Aortic Endovascular Repair

With the rapid evolution of ultrasound technology and the advent of TEE, perioperative dynamic views of the cardiovascular system are now obtainable that have previously been unavailable by conventional transthoracic ultrasonography. Since the esophagus is in close approximation to the aorta, TEE has become an excellent tool for diagnosing aortic pathology. TEE can provide instantaneous views of the aorta and location of the guidewires and endografts prior to deployment, in relation to the normal and diseased thoracic aorta. This imaging modality can also evaluate the endograft location and its success in excluding the diseased aorta from the central aortic flow (24). Pathology of the distal aortic arch and the distal descending thoracic aorta may be accurately visualized intraoperatively. Large intercostal arteries have been imaged, thus avoiding inadvertent obstruction by the aortic stent-graft; however, consistent visualization of intercostal arteries may not be assured in all patients. After stent-graft placement, exclusion of flow from the aorta into the aneurysm can usually be confirmed easily by using Doppler color-flow imaging. Since most of these patients have severe concomitant cardiac disease, TEE allows dynamic assessments of cardiac function. In 1999, we reported our experience with TEE during endovascular thoracic aortic repair (24).

From February to August of 1997, five patients underwent six transluminal endovascular stent-graft procedures for repair of thoracic aortic disease. Patients' ages ranged from 45 – 76 years. After induction of general anesthesia, a multiplane or biplane TEE probe (Acuson, Mountain View, CA) was placed to obtain views of the diseased aorta. Both transverse and longitudinal planes of the aortic arch and descending thoracic aortic segments were imaged. The aortic pathology was confirmed by TEE, and the proximal and distal extent of the intrathoracic lesion was defined. Doppler color-flow imaging was used to identify flow patterns through the aorta before and after stent-graft deployment.

Fluoroscopy and TEE provided guidance for precise positioning of the device across an aortic lesion. Prior to stent-graft placement, a scout angiogram was obtained as a road map for further preliminary endograft positioning. In order to minimize the patient's angiographic contrast exposure, TEE was used in addition to fluoroscopy to confirm that the angiography catheter was properly located proximal to the aortic pathology. While the long-axis view may be used to aid in angiography catheter and delivery device placement, these devices may not be visualized if they are not in the precise plane of the ultrasonic beam. In order to provide imaging of the entire cross-section of the aorta, short-axis images through the aorta were used to confirm the position of this catheter and delivery device.

The endovascular stent-graft delivery system and stent-graft are a unit inserted transfemorally over a stiff guidewire into the aorta. During guidewire, delivery device, and eventually stent-graft deployment, TEE and fluoroscopy were used to assist in proper device placement. The stent-graft delivery system was distinguished from the guidewire by their differences in thickness and echogenicity. Similarly the stent-graft was distinguished from the stent-graft delivery system by its unique echogenic pattern and shadow that is cast by the metallic stent (Fig. 6). By distinguishing the stent-graft from the delivery system, TEE ensured that the endograft bridged the diseased aortic segment. Since dense highly echogenic materials can cause side-lobes, the TEE plane was occasionally rotated 90 degrees in the neck of the aneurysm to confirm that the endograft was located in the correct position. Although TEE could visualize the undeployed stent-graft in relation to the aortic pathology, the TEE probe significantly interfered with fluoroscopic imaging; therefore, TEE could only be used between fluoroscopic examinations. After stent deployment, TEE confirmed proper placement of the endovascular stent-graft across the diseased aorta. Color-flow Doppler was used to exclude any persistent leaks from the aorta into the aneurysm or pseudoaneurysm originating at the endograft margins (see Fig. 7).

TEE was also useful for imaging the longitudinal axis of the thoracic aorta, including side-branches. In Fig. 8, an intercostal artery is clearly visualized by TEE. In addition to demonstrating proper endograft placement relative to the aneurysm, TEE confirmed patency of the large intercostal artery (Fig. 8B).

TEE has distinct advantages over perioperative angiography. TEE may provide exact vessel

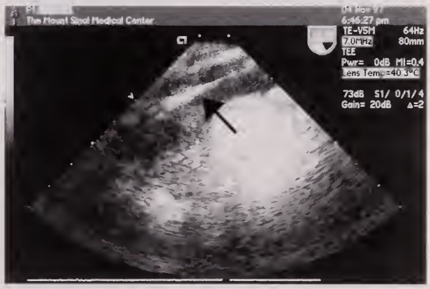

Fig. 6. Long-axis image of distal thoracic aorta during stent-graft delivery system insertion. The stent-graft is seen traversing the aorta in a caudal (left) to cephalad (right) direction. The proximal end stent-graft may be differentiated from the delivery system by the *sudden* change in echodensity (arrow). This interface is at the aneurysm neck and does not occlude the large intercostal artery.

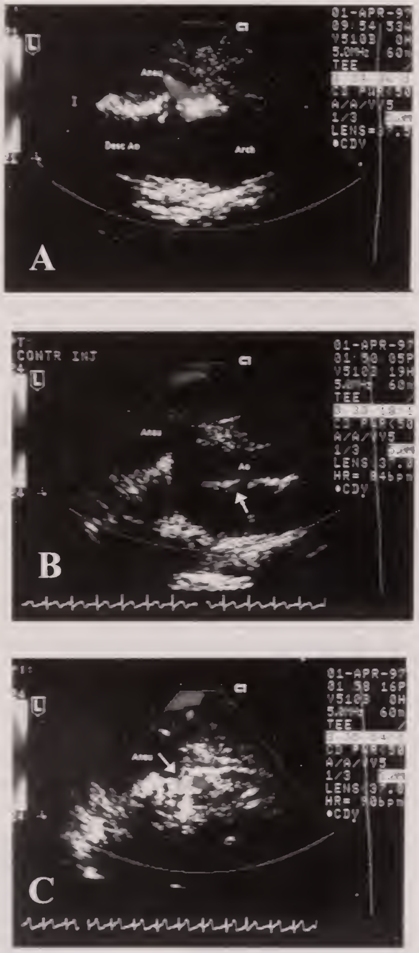

Fig. 7. A. TEE The aortic arch (Arch) and descending aorta (Desc Ao) are labeled. A discontinuity is seen in the distal arch with a communication anteriorly into another contiguous space, which is consistent with a pseudoaneurysm (Aneu). The color-flow Doppler imaging represented by the variated area demonstrates low-velocity blood flow from the aorta entering the neck of this pseudoaneurysm; B. TEE longitudinal image of aortic arch during stent-graft manipulation. The endograft is the larger echogenic tube indicated by the arrow head, and the angiographic "pigtail" catheter is indicated by the arrow; C. TEE longitudinal image of aortic arch after stent-graft deployment. Blood is represented by the variated region in the central aortic lumen. No blood flow, represented by a paucity of color, is seen in the isolated pseudoaneurysm (arrow).

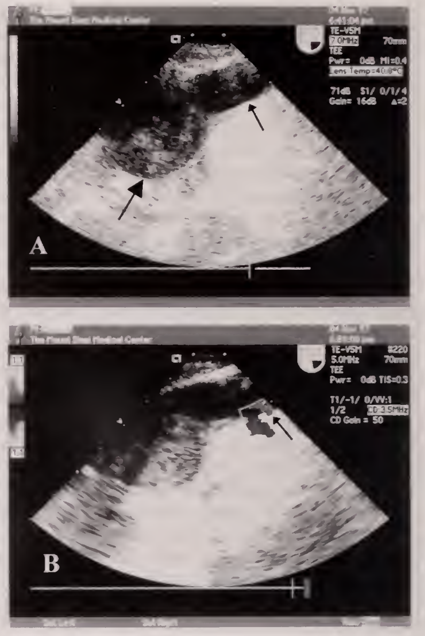

Fig. 8. Baseline longitudinal image of a distal thoracic aneurysm. A. The normal aortic segment is visualized on the right (small arrow) and an aneurysmal dilation is imaged on the left (large arrow) of the image. B. Flow in an intercostal artery (arrow) originating in the posterior aspect of the proximal aortic segment, is demonstrated by Doppler. In color, blue indicates flow away from the transducer while red signifies flow toward the transducer (web site image only).

and lesion sizing and localization, which is difficult to obtain during single-plane angiography. Incomplete exclusion of aneurysms by the endograft as well as iatrogenic aortic dissection may be difficult to detect by angiography. In contrast to angiography, both leakage as well as dissections may be easily diagnosed by TEE. Finally, the real-time function and analysis of perioperative cardiac function provided by TEE may be helpful in the perioperative anesthetic management of this high-risk patient population.

TEE is associated with minimal complications. One drawback is the requirement for general anesthesia with endotracheal intubation for its use in the operating room. Because of the interposition of the trachea and the right bronchus between the esophagus and the aorta, visualization of the distal ascending aorta and proximal aortic arch may be limited (25, 26). In addition, the TEE probe significantly interferes with fluoroscopy; therefore, the TEE probe needs to be partially withdrawn during fluoroscopy.

Complications of Endovascular Aortic Repair

Hypotension during Endovascular Aortic Repair

While endovascular aortic repair is generally less invasive than conventional aortic surgery, positioning and deployment of an endograft in an aorto-iliac system, which contains extensive luminal pathology, may be especially challenging. Acute complications related to infrarenal endovascular stent-graft placement include: (a) migration or malpositioning of the stent-graft, with the possibility of subsequent vessel occlusion or incomplete aneurysm exclusion; (b) distal embolization of arterial plaque or thrombus; (c) abdominal, pelvic or lower extremity ischemia; and (d) acute aortic disruption (27).

Because of the possibility of acute intraoperative aortic rupture, the anesthesiology team must be prepared for the possibility of rapid and extensive fluid resuscitation; this preparation should include the presence of large-bore intravenous access, the availability of rapid fluid infusion systems, direct arterial pressure monitoring, and the placement of central venous monitoring in order to detect early acute changes in preload. Inotropic and vasodilating agents are prepared prior to the case and blood should be immediately available. The use of a central venous catheter versus a pulmonary artery catheter is dictated by the patient's concomitant diseases.

The differential diagnosis of acute hypotension after endovascular stent-graft deployment include sympathetic nerve conduction blockade by regional anesthesia, acute aortic rupture, allergic reaction to angiographic contrast material, or a side effect of adenosine, which may be used during endovascular stent-graft deployment. Adenosine may result in peripheral dilation or hypotension due to high degree AV block. Alternatively, adenosine may cause a brief period of myocardial ischemia, possibly due to hypotension, followed by myocardial pump failure which may have adverse hemodynamic consequences. These effects of adenosine are usually short lived (approximately 10–40 sec) and rare.

Spinal Cord Ischemia during Endovascular TAA Repair

The reported incidence of postoperative neurological injuries after endovascular thoracic aortic reconstruction are similar to that of open thoracic aortic repair. With descending aortic reconstruction, intercostal arteries that supply the anterior spinal cord may be sacrificed, resulting in spinal cord ischemia and injury. Probable risk factors for paraplegia probably include the length of the thoracic endograft placed, as well as a history of abdominal aortic aneurysm repair. In a series of 103 patients undergoing endovascular descending aortic resection, the overall rate of paraplegia/paraparesis was 3% ± 2% (± 70% CL) (28). In the group of 19 patients who required simultaneous surgical repair of an abdominal aortic aneurysm and stent-grafting of the descending thoracic aortic aneurysm, paraplegia occurred in 2 patients, an incidence of 11% ± 7% (± 70% CL) compared to its occurrence in only one patient of the remaining 84, an incident rate of 1% ± 1% (± 70% CL). These differences were not statistically significant. These authors reported that 3 of their 47 patients, who either had previous AAA repairs or presented for concomitant AAA repairs, developed paraplegia, an incidence of 6% ± 4% (± 70% CL), compared to none in those 56 patients with native abdominal aortas. Greenberg et al. reported neurological deficits in 3 of their 25 patients undergoing endovascular descending thoracic aortic repair (29). Patients with longer grafts were identified as having greater risk of postoperative paraplegia. In our practice, patients who are judged to be at high risk for postoperative paraplegia receive perioperatively-induced hypertension (to increase spinal cord blood flow), cerebrospinal fluid drainage (to decrease impedance of spinal cord venous outflow), and steroid and mannitol administration (thought to provide pharmacological protection to spinal cord during spinal cord ischemia) (30).

Post-implantation Syndrome

Post-implantation syndrome is commonly observed after endovascular aortic repair. It is characterized by fever, elevated C-reactive protein levels, and leukocytosis in the absence of an infectious agent. It is usually mild and self-limited, lasting from 2–10 days postoperatively, and responds to NSAID administration. Occasionally, excessive capillary permeability and leakage may lead to life-threatening intravascular hypovolemia and diminished venous return, respiratory failure, and disseminated intravascular coagulation. It is hypothesized that endovascular aortic aneurysm repair induces a significant inflammatory response, resulting in endothelial cell activation from intra-aneurysmal device manipulation (31).

Conclusion

Endovascular aortic repair is a minimally invasive procedure which may offer many advantages over open aortic repair. Immediate technical success can be achieved in at least 80 – 90% of patients presenting for endovascular aortic aneurysm repair. The perioperative mortality is most likely less than conventional surgical repair. Although these procedures are less invasive, complications still arise; these complications tend to be local and vascular (hence easily treatable) as opposed to the systemic complications seen after open repair. Because this technique is still in its infancy, significant experience with long-term results has not yet been compiled. Since arterial rupture is a recognized risk of this procedure, appropriate facilities must be present for resuscitation. Patients undergoing repair of thoracic aortic pathology may be candidates for perioperative TEE monitoring. Since a subgroup of these patients may be at risk for postoperative paraplegia, aggressive spinal cord protection should be considered. Patients with large aneurysms may be at risk for "post-implantation syndrome," characterized by hyperpyrexia, hypotension, and coagulopathy.

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Prediction of Outcome in Cardiac Surgery

Tuula S. Kurki, M.D., Ph.D.

Abstract

There has been growing interest in defining and measuring outcomes for cardiac surgical patients. Outcomes measures have been used in many hospitals as tools for measuring the quality of care, although it is difficult to infer from them how care might be improved. Traditionally, the major outcome endpoints used in cardiac surgery have been the 30-day mortality and morbidity rates. Recently, more innovative intermediate outcomes, including health-related quality of life, functional status, and patient satisfaction 6 months to one year after surgery, have received more attention. A significant proportion of the variance in health care outcomes is affected by patient-related risk factors. By using outcome prediction tools and making conclusions based on preoperative risk factor information, surgeons and anesthesiologists are able to make better decisions about treatment strategies. Additionally, operating room and intensive care unit personnel can use these data to schedule cases and allocate resources more efficiently. These data are also very important for hospital administrators and insurance providers.

Key Words: Cardiac surgery, outcome prediction, risk factors, quality of life, morbidity, mortality.

Introduction

In Western societies, health care costs have been increasing each year. Reasons for this growth include technical and biological advances in medicine and the relative freedom with which hospitals allocate resources to new areas. These costs have been borne by third parties: government, communities, insurance companies, and health maintenance organizations (1). Third parties have now assumed an active role in controlling hospital work, on a cost-benefit basis. As a result, health care systems are under economic pressure. One way of reducing costs in health care is to increase competition, but this raises concerns about reducing the quality of care. Critical and even comparative evaluations of alternative treatment strategies have gained increasing importance. New therapeutic practices have been critically evaluated and older therapies have been re-evaluated in terms of benefits and risks to individual patients. Thus, it is in the interest of patients, health care providers and third-party payers to measure and predict the outcome of different therapeutic approaches. Cardiac surgery has been one of the most intensive areas of research of this type. Patient outcomes between hospitals have been compared for some time. These comparisons may have significant consequences. Thus, the need for valid outcome measures is obvious (2).

All attempts to predict outcome must take into account the variability due to patient-related factors. On one hand, the average outcome of a certain therapeutic intervention depends on the patient population; patients who have high-risk profiles have less favorable outcomes. On the other hand, the same outcome may be viewed differently by different individuals. Ultimately, the measurement of patient outcome is a complex process in which the interests of society (e.g., ability to work) and the individual patient (e.g., quality of life) need to be balanced. The scope of this review is the prediction of outcomes in coronary artery bypass surgery. However, the principles are applicable to other surgical outcomes.

Outcome Dimensions

In cardiac surgery, outcome can be defined as the measurable result of an episode of health care, including all morbid events and mortalities that occur during the 6-month follow-up after cardiac surgery (3). Outcome can be divided into three sub-categories: short-term outcome, intermediate outcome, and long-term outcome. The term "short-term outcomes"

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refers to patient outcomes at discharge or within 30 days of surgery, and includes morbidity and mortality rates, length of hospital stay, resource utilization and patient satisfaction. Patient outcomes at 6 months after surgery are defined as being intermediate outcomes. These (intermediate) outcomes include morbidity and mortality rates, cardiac health status (functional status after treatment), health-related measures of quality of life, patient satisfaction and ability to work. Long-term outcome measurements include quality of life, patient satisfaction, and ability to work for a period of one year or longer (measured up to 10 years) after surgery (3).

Outcome Definitions

Outcomes that require definitions include mortality and morbidity rates, quality of life, patient satisfaction, resource utilization, economic outcome and cost-effectiveness. Mortality is an endpoint that is easy to define. Because patient mortality is a relatively rare event, it is not easy to predict on an individual level. In many institutions, mortality is used as a measure of the quality of care. For coronary bypass surgery, unadjusted mortality rates range from 2.0–4.6% (4). Since underlying diseases are factors contributing to mortality, an adjustment is necessary to compare the effects of treatments on mortality.

Postoperative morbidity is common, especially in cardiac surgery. Since it is a relatively frequent event, it is easier to predict on an individual basis. Morbidity rates vary from 2–43%. Morbidity correlates with length of stay (LOS) in the intensive care unit (ICU) (5), LOS in the hospital, and health care costs (6). Morbidity in cardiac surgery is usually defined as complications that will increase the length of stay postoperatively, either in the ICU or in other areas of the hospital. The most common postoperative morbid events include prolonged mechanical ventilation, ventricular failure, central nervous system complications (e.g., stroke), renal failure, serious infections (e.g., mediastinitis) and severe arrhythmia (7).

Quality of life (QOL) and patient satisfaction are outcomes that are highly valued but difficult to measure objectively. The health-related quality-of-life (HRQoL) instruments are normally categorized as generic or disease-specific, on the basis of their applicability to various conditions. Generic measures are necessary to compare outcomes across different populations and interventions, especially for cost-effectiveness studies. Disease-specific measures assess the special states and concerns of diagnostic groups. There are several commonly used and validated generic measures of QOL, such as the Nottingham Health Profile (NPH), SF-36 health survey, Sickness Impact Profile, Duke Activity Status Index, and RAND Mental Health Inventory. The advantage of generic QOL measurement is that one can compare the impact of various therapies across disease boundaries. The Duke Activity Status Index has been used to measure functional status after cardiac surgery, and the RAND Mental Health Inventory has been used to evaluate emotional health postoperatively (8). One disease-specific measure that has been used to determine HRQoL in coronary artery disease is the Seattle Angina Questionnaire (SAQ) (9).

Economic outcome/cost-effectiveness and resource utilization have generated increasing interest, especially among hospital administrators and insurance companies (10). The evaluation of costs may be based on cost-related events, such as LOS, or on real costs. However, it is not easy to calculate real costs, because the costs of an individual procedure and its possible complications are not always recorded. Moreover, hospital discharge costs may not reflect the costs of the treatment of an individual patient but rather an average of similar or even different procedures as well as the "overhead." Resource utilization includes length of stay in the ICU and hospital, readmission to the ICU or hospital, operating room (OR) time and total hospital costs. Hospitals make comparisons between their operative results in cardiac surgery. The cost-effectiveness analysis should include information about patient satisfaction and quality of postoperative life (QALY) in individual patients. The full analysis should integrate data regarding morbidity and mortality, patient status and patient satisfaction measures, as well as data regarding costs of the care. Comparisons of the alternative modes of care (coronary artery bypass graft [CABG]; with sternotomy and cardiopulmonary bypass [CPB]; minimally invasive CABG; "off-pump" CABG; catheterization laboratory interventions; and medical therapy) (11, 12) can be made based on this information. However, a comparison of newer versus older methods should not be based solely on short-term results. The intermediate or even long-term outcome should be included in such analyses. Changes in the approaches to surgery and anesthesia can also be made based on cost-effectiveness results (13).

Outcome Prediction Tools

Patient risk factors are variables that affect outcome; they are defined as the preoperative patient characteristics that may place the patient at a disadvantage for a favorable outcome. These factors include severity of cardiac disease, co-morbidity factors, general heath status, demographics and socioeconomic factors.

Several risk stratification systems have been developed to predict the risk for mortality and/or morbidity from cardiac surgery. The Montreal Heart Model is one of the first published risk stratification methods (1983) used to determine mortality (14). It was created using data from 500 patients in a single institution. The Parsonnet Model was developed to predict mortality based on a database of 3,500 patients; it was prospectively validated on 1,332 additional patients (15). The Society of Thoracic Surgeons (STS) Database, with 80,000 cardiac surgical patients, was used to develop the STS Model for prediction of mortality and morbidity (16). The STS Model and Parsonnet score are still widely used in U.S. hospitals. The Cleveland Clinic Preoperative Model, developed from a database of 5051 patients and validated on 4069 patients at a single institution, was published in 1992 (17). It consists of 13 risk factors for mortality and morbidity and is also claimed to predict LOS, costs, and the likelihood of early ICU discharge for patient populations. However, none of these models has gained worldwide acceptance in routine clinical planning work, perhaps due to their regional basis and complexity.

Recently, the Parsonnet Model has been tested in several European cardiac surgical centers. Based on the results of these studies, a new modified "Parsonnet" model called "EuroSCORE" has been developed, to predict mortality for both CABG and valve replacement patients (18). The predictive power of this modified index is better for the European patient population than that of the Parsonnet Model. Another new model for use in isolated CABG surgery was developed and validated in 1999 by the Northern New England Cardiovascular Disease Study Group. This model was included in the ACC/AHA practice guidelines for bypass surgery (19, 20).

Accuracy of Outcome Prediction Models

Measurement of Accuracy

Before the risk assessment models are applied to larger populations, the models must be calibrated. We must be able to measure how closely the predicted and observed outcome results match one another. The Hosmer-Lemeshow goodness-of-fit test (chi-square test) has been used to measure calibration (21). Low chi-square values reflect good performance of the model. Another important measurement of the accuracy of the model is how well the model discriminates between ill and healthy patients. A common test to measure discrimination is the C-statistic (22). This statistic is the integral of the receiver-operator characteristic curve (sensitivity versus 1-specificity). A C-statistic of 0.5 indicates that 50% of the outcome could be predicted in the same manner as flipping a coin (which would not be particularly helpful or useful). A perfect test would have a C-statistic of 1.0. Most preoperative risk models have C-statistics of 0.70–0.85.

Statistical Methods

Various statistical methods have been used to predict outcome in cardiac surgery, such as univariate analysis, the Bayesian approach, multiple logistic regression, additive analyses and neural networks. Univariate analysis simply asks whether or not a single risk factor has an association with the outcome under study. These analyses include chi-squares, t-tests, and linear regressions. The results are expressed as p-values. A p-value less than 0.05 means that there is a 95% likelihood that the association between the factor and the outcome is not due to chance.

The Bayesian approach assumes that inferences can be made about future events based upon analyses of past events. It states how posterior probability is calculated using the prior probabilities (23, 24). Bayes' models require some computing and they adjust more easily for rare risk factors and missing data. Bayes' models have been used to predict surgical and non-surgical outcomes in health care.

The logistic regression model, also known as multivariate analysis, is widely used in predictive models. Univariate analyses are first performed to consider the significant risk factors. Then the choice of backward or forward stepwise methods must be made. In the backward method, one factor at a time is removed, and in the forward method one factor at a time is added. After each removal or addition, a beta coefficient or relative weight for that factor is defined. Odds ratios and risk ratios can then be calculated. These ratios are very helpful for decision making. However, the analyses are quite complex and require a computer program to process the data (25).

Neural networks are nonparametric pattern recognition techniques. They use artificial intelligence to determine the probability of a relationship among multiple factors. Studies have been done using neural networks to predict CABG preoperative risks (26).

Additive methods that can be used at the bedside to calculate risk may be developed from logistic regression and Bayesian models. These additive scoring systems are easy to use and provide a rough estimate of the proposed risk. Each significant risk factor is assigned a score corresponding to its influence in the model. The CABDEAL index is an example of an additive model (27).

Development and Application of a Risk Stratification Method

The development of risk indices for cardiac surgery sometimes resembles a search for treasure at the end of the rainbow. While it may not be possible to develop one method that is applicable for all purposes, the methods that attempt to predict the same outcome usually are based on several common factors. Some of our work is summarized to illustrate this approach.

We have previously developed a preoperative risk index for predicting morbidity in coronary bypass patients (27). Data were retrospectively collected from 386 patients who underwent coronary bypass surgery in a single institution. The advantage of using a single institution is that it minimizes variability due to local treatment practices. The relationship between the preoperative risk factors and postoperative morbidity was analyzed using the Bayesian approach. The definition of increased morbidity was a prolonged postoperative hospital stay (greater than 12 days) due to adverse events. The most predictive preoperative risk factors were emergency operation, diabetes, arrhythmia or unstable angina, recent myocardial infarction with low ejection fraction, age greater than 70 years, decreased renal function, chronic pulmonary disease, obesity and cerebrovascular disease. Two types of indices were developed for the prediction of the morbidity. One was a computed model and the other was a manual, additive model with seven risk factors (the CABDEAL). The manual risk index is very easy to use, this ease being a prerequisite for its use in the initial screening of the patients. The risk factors have scores from 1 – 2, and the sum of the total score ranges from 0 – 10 (see Table). If the sum of the score is 2 or less, the risk for postoperative morbidity is minimal. If the score is 3 or more, the risk of postoperative morbidity will increase in a fashion that is nearly linear.

The CABDEAL index was also validated using a sample of 15,383 patients drawn from the New York State Database (28). The method may be used to generate a score that predicts the risk for an individual patient, or for the "normalization" of risk in patient populations. Risk stratification methods may also be useful tools for planning hospital resource allocation, and even pricing. Using the preoperative risk factors of CABDEAL, we have developed a preliminary cost index using the New York State Database. This index predicts increased hospital costs related to postoperative morbidity (6). Work is continuing, to see if the preliminary model is applicable to another type of health care system, specifically in the community-owned and state-subsidized hospitals of Finland.

Clinical Value of Outcome Prediction

Comparisons of the true (observed) and the predicted (risk adjustment) outcomes are used to compare operative results. Hospitals can better allocate their resources if they know their patients' risk profiles preoperatively. They can optimize the scheduling of high-risk patients so as to be prepared for more demanding postoperative care. Currently, surgeons must select different modes of surgical therapy (e.g., CABG with cardiopulmonary bypass, minimally invasive CABG, "off-pump" CABG, etc.), using limited data. By comparing predicted outcomes with observed results, physicians and hospitals can better judge the value of newer and older therapies, and define the patient groups that

TABLE

Preoperative Risk Factor Model (CABDEAL) with Weighted Scores.

C = creatinine > 110 μmol/L	(score 2)
A = age over 70 years	(score 1)
B = BMI > 0.28 or morbid obesity	(score 1)
D = diabetes	(score 2)
E = emergency operation	(score 2)
A = arrhythmia preoperatively or unstable angina	(score 1)
L = chronic lung disease	(score 1)

Total possible score: 10

should receive them. Thus, risk assessment should be part of everyday medical practice (19, 20, 29).

Conclusion

As part of modern "evidence-based medicine," outcome prediction tools, especially risk stratification models, will become widely used in everyday clinical practice. Outcome prediction models will allow a systematic evaluation of preoperative risk among individual patients scheduled for cardiac surgery. In a single institution, outcome prediction will help in selecting the optimal treatment for individual patients, allocating resources, assessing the quality of care on a risk-adjusted basis, and predicting costs. Risk stratification models can also be applied for national or international comparisons of the results of cardiac surgery. Suitable instruments have been developed for the prediction of the outcome in cardiac surgery. Further work is needed to evaluate their accuracy and usefulness in operative planning and financial aspects of operating room management.

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The Open Lung Concept of Alveolar Recruitment Can Improve Outcome in Respiratory Failure and ARDS

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Abstract

Respiratory failure is a common finding in the ICU and in the management of complex cases in the operating room. Over the last ten years, it has become clear that modes of mechanical ventilation and lung recruitment may play a role both in cytokine modulation and patient outcome.

Early lung recruitment and alveolar stabilization may play a very important role in the management of patients with respiratory failure and adult respiratory distress syndrome (ARDS). The open lung concept may be the key to decreasing mortality and morbidity in these patients. This technique not only improves oxygenation, but also affects surfactant function and cytokine modulation.

The open lung concept is physiologically based on the Law of Laplace. Adhering to the principles of the open lung concept, pressure-controlled ventilation may improve patient outcome by reducing the extent of irreversible structural damage to the lungs caused by mechanical ventilation.

Key Words: ARDS, alveolar recruitment, open lung concept, respiratory failure.

Introduction

MECHANICAL VENTILATION is the therapeutic technique most widely used in anesthesiology and critical care medicine for patients in intensive care units (ICU) and those undergoing routine surgery. However, over the last few years, it has become clear that mechanical ventilation with improper settings can lead to a variety of physiological effects which may affect patient outcome, including hypoxemia (1), surfactant depletion (2), cytokine release (3, 4), bacterial transmigration (5, 6), atelectasis (1, 7), and barotrauma.

The mortality rate from adult respiratory distress syndrome (ARDS) has not decreased since it was first described by Ashbaugh (8): mortality rates range from 10–90%, with an average of 50% (9). Various treatments of ARDS have not been very beneficial. These therapies include inhaled nitric oxide (10, 11) as well as administration of antibodies (9). Recruiting and stabilizing collapsed alveoli has also been suggested as a method to prevent and treat ARDS and respiratory failure (12–14). Experimental and clinical studies have clearly shown that techniques using the open lung approach can provide marked improvements in gas exchange. Amato et al. (13) showed improvement in Pa_{O2}, a decreased length of stay in the ICU, and decreased mortality rate. Modes of ventilation and an "open lung" recruitment strategy can reduce time spent on mechanical ventilation, with the additional benefit of decreased ICU costs (15).

Surfactant Changes Due to Mechanical Ventilation

In 1959 Mead (16) reported that dogs that were mechanically ventilated had progressive decreases in pulmonary compliance and that these changes were related to the pulmonary surfactant system. Two primary mechanisms of surfactant failure related to mechanical ventilation have been described. In the first, mechanical ventilation enhances surfactant release from the pneumocyte type II into the alveolus (17). This material is subsequently lost into the small airways as a result of compression of the surfactant film. These changes in alveolar surfactant may affect the permeability of the alve-

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olocapillary barrier to small solutes and protein. The functional integrity of both the endothelium and the epithelium is a prerequisite for maintaining a normal fluid balance at the alveolocapillary membrane; therefore, these changes may cause the increased pulmonary leak observed in respiratory failure with the formation of edema. This breakdown of the barrier function of surfactant may also contribute to the release and modulation of inflammatory mediators (14, 18).

The second mechanism is based on the observation that the alveolar surface area changes are associated with mechanical ventilation, which result in the conversion of surface-active, large-surfactant aggregates into non-surface-active, small-surfactant aggregates (19). Surfactant changes due to mechanical ventilation are reversible as a result of a metabolically active process involving *de novo* production of surfactant. The barrier function of surfactant may collapse with disease and mechanical ventilation, and there may be transmigration of bacteria (3, 20, 21) and cytokine release. Tremblay et al. (3), using isolated lungs, investigated the effect of different ventilation strategies on lung inflammatory mediator expression and production of cytokines tumor necrosis factor$_\alpha$ (TNF$_\alpha$), interleukin-1$_\beta$ (IL-1$_\beta$), interleukin-6 (IL-6), interleukin-10 (IL-10), platelet activating factor (PAF), and interferon-gamma in the presence and absence of a preexisting inflammatory stimulus. The use of high-peak inspiratory lung volumes and the avoidance of positive end-expiratory pressure (PEEP) during mechanical ventilation have a synergetic effort on the release of pro-inflammatory mediators from the lung tissue into the airways. Using 10 cm H_2O of PEEP at comparable peak inspiratory lung volumes or lowering peak inspiratory lung volume when ventilating with zero PEEP reduced these cytokine levels. Therefore, the lung is now being regarded as an important causative part of an inflammation-induced systemic disease state that can evolve to multiorgan failure (MOF) rather than merely a pulmonary disease process. Alveolar collapse with improper mechanical ventilation has been implicated as one of the major causes of poor outcome in mechanically ventilated patients.

Modes of Ventilation that Will Prevent Ventilation-Induced Lung Injury

Since its introduction in critical care medicine more than forty years ago, artificial mechanical ventilation has become a standard lifesaving therapy. It is, however, a topic of much discussion and controversy because artificial ventilation involves a disturbance of normal physiologic function of the lung.

Pressure-Controlled Ventilation

Pressure-controlled ventilation has been a mainstay in the treatment of severe lung disease since it was first described in the neonate by Colgan (22) in 1960. The keystone to proper mechanical ventilation is a pressure-controlled platform, which can be introduced into the operating room and the ICU. Basic physiological principles serve as a rationale for the use of pressure-controlled ventilation (14, 23–25). Since it is well established that artificial ventilation can both cause direct lung damage and modulate cytokine release, it is imperative that we protect the lung from ventilator-induced injury. The cycle of continuous expansion and collapse of alveoli during the respiratory cycle creates a biologic stress. This opening and closing affects structural changes via barotrauma and volutrauma, as well as surfactant function and cytokine release.

If we evaluate mechanical ventilation in light of the basic Law of Laplace, we see that utilizing modes of ventilation which can control both expiratory and inspiratory pressure may be the optimal way to ventilate the lung. The Law of Laplace links the pressure applied by the ventilator to the alveolar pressure (P), which relates surface tension (T) and radius (R):

$$P = 2T/R$$

In a healthy lung, alveolar surfactant minimizes the surface forces at the air-liquid interface, thus guaranteeing alveolar stability at all alveolar sizes. But in mechanically ventilated lungs, there may be varied levels of dysfunction of the surfactant system, because of either direct ventilator effects or the indirect effect of the systemic inflammatory response. The degree of this surfactant damage will determine the amount of pressure needed to expand alveoli from closed to open (Figure).

Pressure-controlled ventilation allows the practitioner to control ventilatory pressure throughout the cycle, in order to generate the pressure necessary to expand alveoli. In true alveolar collapse, the pressure needed for alveolar recruitment may theoretically reach values of 60–70 cm H_2O (26).

Alveolar beds may be opened using a classic wave pattern of pressure control, the decel-

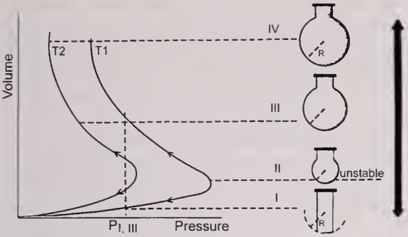


Figure. The open lung concept. Open lung units are more efficient and function at a lower pressure when alveolar radii are larger. The opening pressure is higher when surface tension is elevated (e.g., curve T1 with less effective surfactant). The pressure needed to keep the alveoli open is less when the lung volume indicated by functional residual capacity at IV is compared to that at III and is unstable at I and II. The vertical dotted line labeled $P_{I,III}$ illustrates that it is easier for a partially opened alveolus (III) to be recruited than a closed alveolus (I) at the same pressure. T = surface tension of liquid-air interface; R = radius of alveolus; Law of Laplace: P = 2T/R.

erating wave pattern. This pattern is generated by pressure differences between the inspiratory pressure delivered by the ventilator and the pressure present inside the lung at the beginning of the inspiratory cycle, resulting in minimization of early flow. As the intrathoracic pressure increases, the difference between the ventilator and the intrathoracic pressures diminishes as does the resulting inspiratory flow. This decelerating flow pattern is in contrast to the constant flow pattern used during volume-controlled ventilation. This decelerating pattern opens alveoli better than does a constant flow pattern. The resistance of the airways influences the absolute rate of the respiratory flow; therefore, if the resistance is high, the flow will be reduced, and if the resistance is low, the flow will increase.

An important concept of pressure-controlled ventilation is fresh gas distribution in the lung. When new alveoli are recruited during an inspiratory cycle, the volume necessary to fill these alveoli comes from the ventilator, which is the source of the higher pressure, not from the adjacent lung units, because there is always equal pressure in all areas of the lung. Any reduction in alveolar size immediately results in a flow of fresh gas from the source of highest pressure, which is always the ventilator in the alveolar unit. Decelerating wave pattern ventilation also leads to better pulmonary gas exchange through better gas distribution (23, 26, 27). In contrast to volume control, pressure-controlled ventilation generates no intrapulmonary redistribution of gas from other hyperdistended lung units, the so-called "Pendelluft Effect." Pressure-controlled modes thus always generate an efficient system in which only fresh gas is entering the recruited alveoli (26, 28).

The Open Lung Concept

Gattinoni et al. showed that patients with early ARDS have multiple areas of atelectasis, most commonly in the dependent lung regions, and that this resulted in a reduced volume of the aerated lung (29). Even with the new guidelines of smaller tidal volumes (5 – 7 mL/kg for body weight), we can see that these will generate both barotrauma and biotrauma (cytokine release) in a non-open lung (30, 31). The importance of early lung recruitment and stabilization cannot be stressed enough, for this will affect all aspects of ventilatory physiology; therefore, we must use an "open lung" approach in all mechanically ventilated patients.

The "open lung" concept was first coined by Lachmann (12) and has since been discussed many times. The open lung is one in which there is little or no atelectasis and an optimal gas exchange. Intrapulmonary shunt ideally should be less than 10%, corresponding to a Pa_{O2} of more than 450 mm Hg, when breathing 100% oxygen at sea level (32).

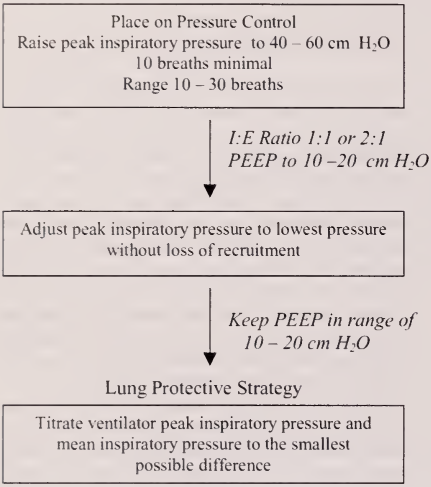
This concept has led in the last few years to an "open lung" procedure, in which the lung is opened and kept open to minimize cyclic forces of alveolar opening and closing. The goal of this technique is to minimize cycle alveolar collapse and reopening. Pressure-controlled ventilation is used with a peak pressure of 40 – 60 cm H_2O and a ratio of the duration of inspiration to that of expiration of 1:1 to 2:1 (Table — I:E ratio). Recruitment success should be checked with a graphic analysis of the pressure volume curve or with blood gas analysis. The peak inspiratory pressure (PIP) is adjusted to the lowest pressure which keeps the lung open. This lowest pressure is realized when the tidal volume remains stable and the arterial blood gases are constant. The ideal pressure is generally 15 – 30 cm H_2O lower than the required recruitment pressure. The positive end-expiratory pressure (PEEP) is set at 10 – 20 cm of H_2O for PEEP to avoid alveolar collapse. This has been used in critical care medicine and in the operating room with great success (13, 33).

TABLE

Open Lung Concept

The goal of the open lung concept procedure is to recruit alveoli and maintain them "open" with the least changes in pressure to minimize alveolar shear forces.

Open Lung Procedure



Place on Pressure Control
Raise peak inspiratory pressure to 40 – 60 cm H_2O
10 breaths minimal
Range 10 – 30 breaths

I:E Ratio 1:1 or 2:1
PEEP to 10 –20 cm H_2O

Adjust peak inspiratory pressure to lowest pressure without loss of recruitment

Keep PEEP in range of 10 – 20 cm H_2O

Lung Protective Strategy

Titrate ventilator peak inspiratory pressure and mean inspiratory pressure to the smallest possible difference

I:E Ratio = durations of inspiration and expiration
PEEP = positive end-expiratory pressure

Amato et al. (13) demonstrated an improved outcome in critically ill patients who had been placed on pressure-controlled modes if they had their lungs opened as compared to those using conventional modes. This group was the first to show a higher weaning rate based on the mode of ventilation used. Amato et al. were very careful to construct a pressure-volume curve for each patient and used it as the keystone in the management of the patient. Preliminary results of our study, monitored by the Food and Drug Administration (FDA), in which the open lung concept was used with patients soon after admission to the critical care units of the University of Rochester, indicated that the mortality rate was 10% in a group of 22 patients with severe ARDS (Pa_{O2}/FiO_2 ratios of less than 150). We also noted that the incidence of multiple organ dysfunction syndrome (MODS) in this patient population was less than that of historical controls (34). These studies may support the approach that it is wise to spend extra time at the onset of mechanical ventilation to find physiologically based ventilation settings, as opposed to using standard settings for every patient (35).

The results of studies using open lung may be due to decreased barotrauma and biotrauma (cytokine) modulation. The open lung concept suggests that barotrauma and biotrauma are more dependent on swings in airway pressures that are generated when alveoli open and close, rather than on the absolute peak inspiratory pressure (37). This ability of alveoli to remain open modulates the surfactant system and does not allow for ongoing collapse due to loss of surfactant as the result of cyclic changes with inspiration and expiration (14). Finally, the most important contribution may be that an open lung may be less likely to produce biotrauma to itself and other organ systems, thus decreasing cytokine load and the systemic inflammatory response.

Summary

The use of the open lung concept may favorably alter a variety of physiologic responses to improve patient outcome in the operating room and in the ICU. The core of this strategy is the understanding that alveolar atelectasis is detrimental and can promote a systemic inflammatory response. Maintaining alveolar beds and keeping them open during mechanical ventilation is an important therapeutic goal.

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Recent Advances in Airway Management

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Abstract

Airway management is a critical component of modern anesthetic care. Advances in airway management, as well as the recent history of airway management teaching at The Mount Sinai Hospital, are reviewed.

Key Words: Airway management, Bullard laryngoscope, cuffed oropharyngeal airway, esophageal-tracheal Combitube, flexible fiberoptic laryngoscope, laryngeal mask airway, unanticipated difficult airways, Wu laryngoscope.

Approximately one-third of all adverse anesthetic outcomes are related to respiratory problems (1), and almost one-third of all anesthetic-related deaths result from an inability to manage the difficult airway (2). Airway patency for oxygenation and ventilation remains a pivotal point in modern anesthesia practice. Failure to provide the patient with an adequately patent airway leads to cerebral hypoxia, rapid deterioration and, possibly, death.

In an effort to help prevent airway-related morbidity and mortality, the American Society of Anesthesiologists published practice guidelines in 1993. An algorithm is provided to facilitate handling of the difficult airway (3). The first portion of the algorithm addresses the anticipated difficult airway. Unfortunately, despite all the information currently available, no single factor reliably predicts difficulties; consequently, many difficult airways are not recognized until after induction of general anesthesia (4). These airways are termed the "unanticipated difficult airways." Care of patients presenting with unanticipated difficult airways relies on both invasive and noninvasive techniques. Noninvasive techniques are discussed below.

Masks

Facemask ventilation is the most frequently applied of all modern techniques. This method is generally the first one learned and the first one applied. Unfortunately, facemask ventilation is frequently difficult to achieve. Successful facemask ventilation depends on airway patency. Commonly, when the patient is in the supine position, the base of tongue falls posteriorly and obstructs the airway. Chin lift, jaw thrust, and oral or nasal airways generally overcome this impediment. Facemask ventilation is fraught with potential complications. One of the most frequent and serious complications is gastric insufflation. Forcing gas into the stomach predisposes the patient to two important problems: aspiration pneumonitis and ventilatory embarrassment. Maintaining airway patency and utilizing inspiratory pressures of less than 20 cm of water help prevent introducing gas into the stomach.

In 1983, Brain (5) first described a new mask (Figure), the laryngeal mask airway (LMA). LMAs have been commercially available in the United States since 1992 and have met with great success. As the name implies, laryngeal mask airways are masks that fit around the larynx. In contrast to endotracheal tubes, LMAs do not enter the larynx, vocal

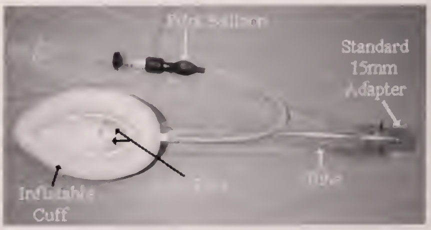

Figure. Classic laryngeal mask airway.

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cords, or trachea. As with the face mask, gas leaks are common around the LMA. Current models are constructed from silicon, thereby removing the potential for latex allergies, and are available in a variety of sizes designed to fit everyone, from the smallest to the largest. Various LMA models provide reinforced tubes to prevent kinking, are nonmetallic for use with magnetic resonance imaging, facilitate endotracheal intubation, or divert regurgitated gastric content away from the trachea.

LMA insertion requires ablation of gag reflexes. Those who would otherwise not tolerate airway manipulation are poor candidates for LMA placement. With the patient's head in the sniffing position, the operator opens the patient's mouth. The convex portion of the LMA is placed against the hard palate, and the device is inserted around the base of the tongue until it abuts the upper esophageal sphincter residing at the bifurcation of the digestive and respiratory tracts. The balloon is inflated, and the airway's 15-mm adapter is connected to a source of oxygen. Signs of proper placement include chest wall motion, breath sounds over both lung fields, absence of sounds over the epigastrium, and a capnogram which measures the concentration of CO_2 in the end-tidal gas. Ideal placement excludes the epiglottis from the anterior (concave) mask surface; nevertheless, the epiglottis sometimes flips into the bowl of the mask without producing significant airway obstruction. At other times airway obstruction is considerable. Correct placement does not affect vocal cord movement, so patients may vocalize while an LMA is in place.

Positive pressure ventilation may be impaired by improper placement of the LMA (6). If oxygenation and ventilation are unacceptable, the device should be removed and replaced. Variations in placement techniques are useful when difficult insertions are experienced. Alternative techniques include slight inflation of the cuff prior to insertion (7), jaw thrust (8), tube rotation (9), and elevation of the base of the tongue with a laryngoscope blade (10). When inspiratory pressures exceed 20 cm of water, gas tends to leak around the inflatable cuff. However, an audible leak does not contraindicate use of LMA if adequate oxygenation and ventilation can be achieved without dilating the stomach. LMAs have been used successfully in anesthetized patients for 7 hours (11), but this author is reluctant to recommend such a practice. Studies on anesthetized patients reveal successful insertions on the first attempt in 88–90% of patients and on the second attempt in 95–98% of patients (12). Hypertension and tachycardia associated with LMA insertion are minimal (12) and compare favorably to tracheal intubation (13).

Contraindications to the LMA are relative and include poor pulmonary compliance and limited interincisor distance, as well as increased risk of aspiration pneumonia. Contraindications to its use must be weighed against its potential benefit during a particular clinical situation. Inability to achieve sniffing position may complicate insertion, but does not contraindicate LMA use. Small mouth openings complicate placement, but theoretically interincisor distances of 1.5 cm or greater allow for insertion. Pharyngeal abnormalities such as tonsillar hypertrophy, hematoma, abscess, or mucosal lesions may hamper advancement of the LMA into the retropharyngeal space. When correctly placed, an LMA approximates the upper esophageal sphincter, but does not occlude the esophagus. The inflatable balloon around the mask does not reliably exclude vomitus from entering the trachea (14). Many malpositions that allow oxygenation and ventilation can incorporate the esophagus into the LMA; consequently, patients at increased risk for aspiration pneumonitis are not good candidates for LMA use (15). Although cricoid pressure may be used to occlude the esophagus and prevent gastric contents from reaching the pharynx and trachea, its application may impair LMA insertion. If LMA use is deemed to be the method of choice in a patient at risk for aspiration pneumonitis, ventilation may be continued with simultaneous application of cricoid pressure. However, if cricoid pressure interferes with oxygenation and ventilation, it must be released. Any one of multiple malpositions of the LMA can result in gastric distention, increasing the risk of regurgitation and vomiting. The insertion of a gastric tube prior to using an LMA often treats gastric distention and prevents its recurrence. In 1999, a new LMA model was released that provides an esophageal port for evacuation of esophageal contents.

In an emergency, oxygenation and ventilation must receive top priority. LMA should be employed despite its relative contraindications, since its placement is the fastest and most efficient technique of establishing airway patency. Examples of such emergency situations theoretically include cardiac arrest and rapid cardiopulmonary decompensation in patients with difficult airways. Alternative methods can be substituted on an elective basis.

Since 1983, LMAs have been the only means of providing laryngeal mask ventilation. In 1998 Benumof described the Glottic Aperture Seal (GAS) airway (16). The GAS airway provides a firm glottic pad that is pressed up against laryngeal cartilages, forming a tight seal between the device and the larynx, thereby allowing both greater inspiratory pressures in patients with poor pulmonary compliance and the exclusion of vomitus from the trachea. At this time, it is not commercially available.

The pharyngeal airway (PA) is a mask-like device, which became commercially available in October 2000. The PA provides an inflatable pharyngeal cuff to prevent gas from escaping through the nose and mouth. It also offers a gilled tip that is designed to seal the esophagus.

Retraction Laryngoscopy Blades

Tracheal intubation is frequently accomplished utilizing a curved Macintosh (17) or straight Miller (18) laryngoscope blade. Sometimes, one or both of these blades fail to provide adequate visualization of the larynx. Recent advances in retractable-blade design include the Bullard (19) and Wu (20) laryngoscopes. Both systems combine the advantages of fiberoptics with the durability of traditional steel blades. The fiberoptic system directs light around anatomic structures; therefore, use of these blades does not require that the patient be in the sniffing position. These systems may be particularly helpful for patients with ankylosing spondylitis, cervical vertebral instability, prior cervical fusions, or severe arthritis. As with all fiberoptic devices, they offer a limited field of view that is further restricted by blood or secretions.

The Bullard laryngoscope (Circon Corp., Santa Barbara, CA) offers a broad but thin retraction blade with a fiberoptic system running along its back portion. A tracheal tube is loaded onto its stylette, and the device is inserted blindly into the mouth, around the base of tongue, and underneath the epiglottis. After positioning, the laryngoscope is lifted anteriorly to expose the vocal cords, and the tracheal tube is advanced over the stylette into the trachea. If the blade lodges in the vallecula, the epiglottis is not lifted and glottic visualization is impeded. Sometimes it is difficult to advance the tracheal tube over the stylette between the vocal cords.

The Wu laryngoscope (Achi Corp., Fremont, CA) offers a bi-valved blade that allows visualization and manipulation of the tracheal tube through its hollow center. It is probably of most value for patients with large tongues, masses encroaching upon the airway, or redundant tissues; however, the blade is large and takes some practice to use comfortably.

Flexible Fiberoptic Laryngoscopes

It has been the author's personal experience that flexible fiberoptic laryngoscopes have been used successfully in many difficult intubations. Their unequaled flexibility allows for intubation of patients, without the need for head and neck manipulation. Fiberscopes may be used for both oral and nasal approaches to the larynx. They virtually eliminate laryngoscopy-associated dental damage and unrecognized esophageal intubation. They have been used successfully in patients with small mouth openings, provide cardiovascular stability during manipulation, and there has been excellent patient acceptance. Their major disadvantages are their limited field of view (which is exacerbated by blood and secretions in the airway) and the high cost of purchase and maintenance.

Recent advances in fiberscope technology have provided improved optics and greater portability. Modern optical systems offer a larger field of vision with wide-angle lenses. Most recently, battery-powered fiberscopes have become available, allowing for convenient transport to any area within the hospital. They obviate the need to carry heavy illuminators and do not require an outside alternating-current source.

Esophageal-Tracheal Combitubes

Over the years, numerous esophageal devices have been designed for airway management. Until recently, the best-known instrument was the esophageal obturator airway. Problems associated with the esophageal obturator airway include difficult mask fit, accidental tracheal intubation producing complete airway obstruction, vomiting, and esophageal rupture.

In 1988, the esophageal-tracheal Combitube (Tyco International-Kendall Health Care Products Company, Mansfield, MA) was approved for use in the United States. Combitubes are double lumen tubes that provide oxygenation and ventilation in the esophageal or tracheal position. Initially designed by Michael Frass, an intensivist in Vienna, Austria, the Combitube was intended as an airway patency device to be used by first responders to an emergency cardiac arrest when these responders lack traditional airway-maintenance skills (personal communication, October 1990). The Combitube's success in these emergency situations has expanded its applicability. It is now used as an alternative device for the management of difficult airways and has been used for elective surgery in patients who rely on their voices professionally, such as singers, lecturers, actors, and attorneys.

The Combitube has a few disadvantages. They currently come in two adult sizes, but no pediatric versions. Pulmonary toilet is not possible in the esophageal position. Esophageal rupture has been reported after its use (21).

Cuffed Oropharyngeal Airway

Guedel airways remain a classic airway management tool. In 1992, Greenberg and Toung (22) described modifications of Guedel's airway that may provide some advantages. The Cuffed Oropharyngeal Airway (COPA) (Mallinckrodt Corp., St. Louis, MO) consists of an inflatable balloon on the proximal end, with a 15-mm standard airway adapter affixed to the other end. The inflated balloon serves to displace the base of the tongue anteriorly, create an air-tight seal with the pharynx, and lift the epiglottis off the posterior pharyngeal wall. The 15-mm adapter allows direct connection to a standard respiratory circuit. COPAs are constructed of polyvinyl chloride and are disposable after a single use.

Advanced Airway Management Teaching at the Mount Sinai School of Medicine

In 1990, the Mount Sinai School of Medicine led the way in teaching new airway techniques. At that time, Mount Sinai was one of only two institutions worldwide to offer formal residency training in advanced airway management. By 1995, many training programs had followed this lead, but formal training in advanced airway management remained neglected by most other anesthesia residencies in the United States (23). In 1998, the program was discontinued due to the decreasing number of residents in the anesthesiology program. From 1990–1998 most residents developed fiberscope skills, well beyond those of residents who graduated prior to 1990 (personal observation). This program has placed 122 practicing physicians among the small cadre of anesthesiologists who are schooled and skilled in the use of advanced airway devices. In addition, some anesthesiologists have extended their expertise to devices other than flexible fiberoptic laryngoscopes.

Today, difficult airway management is commonly taught as clinical situations arise. Because these difficult clinical situations are infrequent and sporadic, opportunities to teach and practice the necessary skills are limited. Learning based on sporadic and occasional occurrences is usually incomplete and non-uniform. Lectures, "difficult- airway" workshops, manikin practice, and simulator sessions cannot replace actual clinical experience. All anesthesia residency programs are encouraged to institute formal training in advanced airway management.

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Strategies for Minimizing the Use of Allogeneic Blood During Orthopedic Surgery

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Abstract

Selected orthopedic surgical procedures, such as total joint arthroplasty and spinal instrumentation, have some of the highest perioperative transfusion rates of all surgical procedures. Blood transfusions carry the risk of complications, including the transmission of disease, immunomodulation, and hemolytic and non-hemolytic reactions. Strategies that reduce or remove the risk of allogeneic transfusion include preoperative autologous donation, acute normovolemic hemodilution, perioperative cell salvage techniques, deliberate hypotension, and pharmacologic interventions. This paper will review the current status of these therapies in the orthopedic surgical patient.

Key Words: Orthopedic surgery, allogeneic blood transfusion, hemodilution, red cell salvaging techniques.

Preoperative Autologous Donation

PATIENTS MAY CHOOSE to have their own (i.e., autologous) blood processed and stored in the weeks prior to their intended surgery. While advanced age had been considered a relative contraindication to predonation because of the presence of anemia and concurrent diseases, a study of 1,073 patients over 65 years of age revealed an incidence of cardiac and vasovagal complications of only 0.6% (1). In fact, studies of predictors of vasovagal reactions during blood donations reveal that younger age, lower weight, and first-time donations, rather than repeat donations, were the independent predictors for the risk of vasovagal reactions (2). Anginal and vasovagal events requiring hospitalization after blood donation do occur at a 12-fold higher rate for autologous donation (0.006%) than for allogeneic donation (0.0005%), with first time donation in the autologous group being, again, identified as a risk factor (3).

The availability of autologous blood does not ensure that the patient will not experience adverse reactions associated with transfusion. Over a 6-year period, the experience of one large academic medical center revealed that 12 of 27,859 (0.0435%) transfusion reactions were associated with preoperative autologous donation (PAD) and transfusion. These reactions included one episode of acute hemolytic transfusion reaction secondary to clerical error and four allergic transfusion reactions (two of which occurred in patients who had a history of allergy to plastic and/or latex, which are found in blood collection bags). Five febrile non-hemolytic reactions and two non-febrile, non-hemolytic reactions occurred, but were not associated with positive blood cultures (4).

PAD has been shown to alter transfusion patterns. Early studies demonstrated that the availability of autologous red cells resulted in more conservative approaches to transfusion. PAD was effective in protecting 77.6% of 134 patients undergoing orthopedic surgical procedures from exposure to allogeneic blood (5). More recently, several studies have found that even though allogeneic transfusion rates were greater in patients who did not predonate blood, overall transfusion occurred more frequently in those who had PAD than in those who did not (6, 7). This is probably related to lower preoperative hematocrits in those patients who predonated, and may reflect a more liberal transfusion policy when autologous blood is available. The Practice Guidelines for blood component therapy (8), developed by the American Society of Anesthesiologists Task Force, state that "the indications for transfusion of autologous red blood cells may be more liberal than for allo-

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geneic red blood cells because of the lower (but still significant) risks associated with the former."

PAD in orthopedic procedures has not been determined to be cost effective, with a calculated cost of $235,000 per quality-adjusted year of life saved by avoidance of transfusion-associated infectious disease (9). It is more expensive to produce an autologous unit, due to the costs involved with collection (scheduling donations, longer screening interviews of patients with complicated histories), special labeling, and storage considerations. Costs are also incurred with the disposal of unused PAD units, more than half of which are discarded. Patients may not meet requirements of community volunteer donors. Units may become outdated since they are donated weeks before the planned procedure and must be available until the patient is discharged from the hospital. Healy et al. found PAD to be cost-effective if one considers the expense incurred by longer hospitalizations necessary to treat postoperative infections that result from the immunosuppressive effects of allogeneic blood (10). The incalculable benefits associated with decreased anxiety of patients regarding allogeneic transfusion will continue to make PAD a principal intervention.

Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) requires the withdrawal of whole blood at the beginning of a surgical procedure and its simultaneous replacement with crystalloid or colloid solution, to maintain intravascular volume. Blood is removed into sterile citrate-containing bags according to the formula by Gross:

$$\text{volume to be removed} = \text{EBV} \times \frac{\text{initial Hct} - \text{minimum allowable Hct}}{\text{average Hct}}$$

where EBV is estimated blood volume and Hct is hematocrit (11).

The units of whole blood are stored with the patient, thereby eliminating the possibility of clerical error. It is thought that dilution decreases the number of red cells lost for each volume of blood shed during surgery. Thus, ANH conserves red blood cells. This technique is inexpensive and convenient, and it preserves all of the components of autologous blood.

Decreased viscosity of blood with a hematocrit of 5 g/dL is associated with decreased systemic vascular resistance and increases in heart rate, stroke volume and cardiac index in healthy volunteers (12). Reductions of hemoglobin to 7 g/dL resulted in no detectable changes in cognitive function in 9 healthy volunteers, but further reductions to 5 g/dL did cause reversible increases in reaction times and impairments in immediate and delayed memory (13).

Patients undergoing surgery, with or without ANH, experience small changes in prothrombin time and partial thromboplastin time, and increased concentrations of prothrombin fragment 1ß2 and thrombin-antithrombin III complex (markers for coagulation), and D-dimer and plasmin-alpha 2-antiplasmin complex (markers for fibrinolysis). Surgery itself can activate both the coagulation and fibrinolytic systems secondary to inflammation and to the mobilization of fat and bone debris. Thus, ANH has not been implicated in the derangement of hemostasis that accompanies it (14). Interestingly, Bombardini et al. found a 13-fold reduction in fatal pulmonary thromboembolism in 4,653 patients who underwent elective orthopedic surgery with ANH, to hemoglobin levels > 6 g/dL, compared with a non-ANH cohort (15). This may be secondary to the depletion of coagulation factors, increased regional blood flow or improved rheological properties of the blood.

Ness et al. randomized 50 patients to donate PAD of 3 units of red blood cells or to undergo ANH prior to radical retropubic prostatectomy (16). They found that ANH could safely replace or augment PAD as a means of decreasing the use of allogeneic blood, and they consider their results applicable to any surgical procedure in which a 1,000 mL blood loss is anticipated. In a randomized trial of patients undergoing total knee arthroplasty who predonated either one unit of blood for unilateral, or two units for bilateral knee procedures, or who underwent ANH to a hematocrit of 28%, Goodnough et al. found no differences in the amount of allogeneic blood transfusions among the PAD and ANH cohorts, for all 32 patients (17). Conversely, a meta-analysis of all 24 eligible prospective randomized trials (1,218 patients) comparing ANH with control groups was undertaken. ANH effectively reduced the likelihood of exposure to at least 1 unit of allogeneic blood in cardiac and miscellaneous procedures, but not in orthopedic surgery. The overall results of this analysis were inconclusive since sample sizes in the trials were small, variable amounts of blood were withdrawn (18), and trials involving different surgical procedures had to be pooled.

Perioperative Red Cell Salvage

Perioperative red cell salvage (PCS) is a technique that has been widely used in the United States and Europe since the 1970s. It involves the collection and reinfusion of red cells lost during and after surgery. Intraoperative salvage during orthopedic surgical procedures involves washing prior to reinfusion to remove the bone, fat, hemolytic byproducts, methylmethacrylate monomer, and other debris. The use of this technology had been shown to be effective in reducing allogeneic blood use, and also reducing the risk of transmission of infectious disease and preserving the allogeneic blood reserves (19). The use of allogeneic blood was investigated in a meta-analysis of 16 studies in which patients were randomized either to undergo, or not to undergo, PCS for orthopedic surgery. Huet et al. found that devices that wash, or do not wash, salvaged blood both decrease the proportion of patients who require allogeneic transfusion (20).

Advantages of PCS include avoiding the cost and inconvenience of repeated preoperative donations and of discarding blood. Its use is precluded when blood is contaminated with bacteria or tumor. Hansen et al. recovered malignant cells in blood salvaged from 57 of 61 patients undergoing oncologic surgery; only 26% of those patients had evidence of circulating malignant cells (21). He showed, *in vitro,* that irradiation of salvaged blood with gamma radiation was effective in inactivating tumor cells from salvaged blood (22). Continued research may provide a basis for the use of cell salvage during orthopedic oncologic procedures.

Postoperative blood salvage devices collect blood from surgical drains, with reinfusion without processing; this blood may contain cytokines, free hemoglobin and debris. The utility of postoperative devices had been challenged by Umlas et al.(23), who found that in 51 patients undergoing hip or knee arthroplasty, the red blood content of drainage of the first 6 postoperative hours was small (55 ± 29 mL for hip and 121 ± 50 mL for knee replacements). They determined that the potential annual national expenditure for 6-hour collections of this low volume of blood return would be approximately $31 – 35.5 million dollars. Thus, the cost of the devices does not justify routine use, and may only be indicated for use during bilateral joint replacements.

Deliberate Hypotension

Controlled hypotensive anesthesia can be achieved by decreasing vascular tone or cardiac output. The reduction in mean arterial pressure (MAP) has been associated with reduced blood loss and relatively bloodless operative fields, which may contribute to decreased operative times. In orthopedic procedures, another potential advantage is that the reduced amount of blood in the cement-bone interface during total joint arthroplasty may improve the quality of fixation of the prosthesis to the bone.

Hypotensive techniques have been shown to be particularly effective in reducing transfusion requirements in patients undergoing spinal surgery. One hundred forty-five patients undergoing spinal surgery, in whom the mean arterial pressure (MAP) was reduced by 20 mm Hg, experienced a 50% reduction in blood loss and a 36% reduction in the need for blood replacement (24). Lawhon et al. studied 264 posterior spinal fusions in adults in whom hypotension to a MAP less than 80 mm Hg was achieved using nitroprusside or trimethaphan; they found that blood loss was reduced by 33% (25).

Greater levels of hypotensive anesthesia have been advocated to further decrease blood loss. Sharrock et al. (26) randomized 40 patients undergoing primary total hip arthroplasty to target MAPs of 50 or 60 mm Hg. They found a significant decrease in intraoperative blood loss in the 50 mm Hg group, with subjective improvements in the amount of surgical bleeding during the dissection of the hip joint and reaming of the femur and acetabulum. Hypotensive epidural anesthesia to MAPs of 45 – 55 mm Hg has been shown not to affect cognitive function, including memory, psychomotor and language skills, in a study of elderly patients undergoing elective primary total hip replacement (27).

Complications of hypotensive techniques include reactionary hemorrhage, persistent hypotension, and cardiac ischemic injury. Ischemic optic neuropathy (ION) has been described following orthopedic (particularly spinal) surgery (28 – 30). Etiologies of ION may include lower mean blood pressure (from deliberate hypotension) and increases in intraocular pressure (from positioning) which could result in lower perfusion pressure to the optic nerve head. Hypoxia leads to destruction of axonal integrity, and free radicals that accumulate during reperfusion from ischemia may further damage the optic nerve. Patients who have a small cup-to-disk ratio (associated with compression of structures secondary to swelling) may be anatomically predisposed to developing ION (31). The American Society of Anesthesiologists has created a postoperative visual loss registry to collect information regarding ocular complications from non-ophthalmologic surgery in an attempt to determine the parameters that contribute to the occurrence of ION.

Pharmacological Interventions

Recombinant human erythropoietin is a glycoprotein that stimulates erythropoiesis. Four hundred ninety patients who were scheduled to undergo total joint arthroplasty were randomized to either preoperative erythropoietin or PAD groups (32). The patients who received erythropoietin had fewer transfusions with allogeneic blood and had significantly higher mean hemoglobin levels both preoperatively and on the first postoperative day. The widespread use of erythropoietin, however, is limited by its high cost. Economic analysis revealed that use of erythropoietin alone in orthopedic surgery patients led to only modest incremental benefit compared with no intervention. Thus, the routine use of erythropoietin is not justified (33).

Antifibrinolytic agents have been employed to reduce blood loss during orthopedic surgery. A single dose of 10 mg/kg of tranexamic acid administered to patients undergoing total knee arthroplasty, prior to the release of the tourniquet, was associated with a significantly decreased mean blood loss and the need for fewer transfusions (34, 35). Aprotinin, a serine protease inhibitor, is usually administered as 2 million kallikrein inhibitor units (KIU) prior to surgery. Lower doses have proven effective in reducing blood loss during cardiac surgery (36), but doses of 20,000 KIU/kg do not seem to be effective for patients undergoing primary unilateral hip arthroplasty (37).

Combination Therapies

Multiple studies have looked at the advantages of combining blood conservation strategies. The use of erythropoietin allows the safe predonation of more autologous units of blood than can be deposited without it (38). The combined use of PCS, PAD, and hypotensive anesthesia prevented the need for allogeneic blood in 50 patients who underwent spinal instrumentation and fusion (39). Blais et al. added the use of apheresis (red cells, plasma and platelet concentrates) to ANH and intraoperative cell salvage, and compared this combination of techniques to both the use of intraoperative cell salvage alone and to a retrospective cohort of patients who received conventional transfusion therapy. They found that the combination of strategies decreased the quantity not only of allogeneic red cells transfused, but also of other blood products in those patients undergoing reconstructive spinal surgery (40). Schmied et al. (41) looked at the effect of red cell scavenging, hemodilution and active warming in 821 elective total joint arthroplasties. Both univariate and regression analyses indicated that each treatment contributed to a more than twofold reduction in transfusion requirements. By combining PAD, PCS, and hemodilution, Borghi et al. were able to restrict the use of allogeneic blood to only 184 of 2,303 (8%) of patients undergoing major orthopedic procedures over the last twenty years (42).

In the future, combined therapies may include "augmented acute normovolemic hemodilution." This term describes the use of one of the new oxygen-carrying solutions (either stroma-free hemoglobin or perfluorocarbon emulsions) instead of currently-available crystalloids and colloids for maintaining intravascular volume during ANH.

Conclusions

Many therapies and techniques are available to prevent or reclaim the blood lost during orthopedic surgical procedures. Understanding the advantages and limitations of these interventions permits their rational use and can markedly decrease or obviate the need for allogeneic transfusion. Cooperation between anesthesiologists and surgeons in identifying and enrolling patients is an integral part of a successful blood conservation program.

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Latex Allergy

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Abstract

IgE-mediated allergy to natural rubber latex is a new health hazard about which information has been evolving for the past decade. This sensitivity poses a particular threat to children with congenital malformations or a history of multiple surgical interventions, and to individuals with high workplace exposure, such as health care workers. The only currently available treatment is complete avoidance of latex, which may require a change of workplace and loss of career. Latex allergy can lead to chronic occupational asthma, anaphylaxis, and even death. Preventive measures must be taken, in part because no treatment is available. This article provides an overview of latex allergy, and recommends some measures that may prevent its continuing dissemination and reduce its life-threatening risk.

Key Words: Latex allergy, environmental allergy, occupational allergy.

Introduction

THE EMERGENCE of a new medical entity is a rare event and is often met with skepticism. However, the number of people experiencing serious allergic reactions to latex has increased significantly since the late 1980s. Prior to that time, latex was not considered to be an allergen. Now, however, it is apparent that latex allergy poses a major problem for an increasing number of patients, health care workers, and institutions, often threatening both health and livelihood. So why the cynicism about latex allergy? It may simply be a reaction to the word "allergy." Many individuals who are not susceptible to allergies look upon any allergy as a sign of weakness of body or mind, as a deception by those trying to evade work or responsibility, or as more nuisance than anything else. Doctors tend to disbelieve anything they didn't learn in medical school, with a kind of rigidity that many would like to attribute only to the "older generation." This particular allergy should be of special interest and concern to anesthesiologists who treat patients with this condition at an especially vulnerable time, in the operating room, and who are themselves at high risk of developing latex allergy. For a more in-depth examination of latex allergy, please see the article by Brehler and Kutting (1).

What Is Latex Allergy?

Patients and health care workers are regularly exposed to significant amounts of natural rubber latex from latex gloves. There are three categories of reactions to gloves worn as barrier protection (Table 1). Unfortunately, these are often grouped together as "latex allergy" or "latex glove reactions." Irritant dermatitis is an entirely non-immunologic response to glove use, and allergic contact dermatitis is a type IV or cell-mediated immunologic response to the chemical additives (including thiurams and carbamates) used to process most gloves; therefore, while these adverse reactions are byproducts of glove use, they are not symptoms of latex protein allergy. The immediate hypersensitivity IgE-mediated latex-protein reactions (type I) are the only reactions that are truly latex allergies. This immediate hypersensitivity is the only reaction to latex that is life-threatening and that has many effects that reach far beyond the localized area of exposure.

Signs and symptoms of latex allergy include eczema, contact and generalized urticaria and rhino-conjunctivitis. More serious reactions include asthma, anaphylaxis, and even death. The dose of allergen, route of exposure, and individual sensitivity influence the type and severity of the reaction. According to the American Academy of Allergy, Asthma & Immunology (AAAAI), the greatest danger of severe reactions occurs when latex comes in contact with moist areas of the body or internal surfaces during surgery, because more of the allergen can be absorbed into the body (2). Since intact skin provides a good barrier, the absorption of latex

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TABLE I

Glove Reactions

Reaction	Clinical Manifestation	Mechanism	Antigens	Diagnosis
Irritant	Skin red, dry, does not extend beyond contact site	(non-immune)	None	
Type IV Delayed	Skin red, dry, pruritus at site of contact, eczema, erythema, weeping, vesiculation, may extend beyond contact site	Cell-mediated	Manufacturing additives	Patch testing
Type I Immediate	Eczema, urticaria, angioedema, laryngeal edema, asthma, rhinitis, anaphylaxis	IgE	Small MW latex proteins	SPT, RAST, provocation testing

MW = molecular weight; RAST = radioallergosorbent test; SPT = skin prick test.

allergens is facilitated when this protective barrier is compromised, as with contact dermatitis or open wounds, thereby increasing the likelihood of an allergic reaction.

The respiratory tree is another important port of entry. Cornstarch lubricating powder adsorbs latex proteins during the glove manufacturing process. When these particles are aerosolized during routine glove use, everyone in the immediate area is exposed to latex without obvious contact.

A third route for high exposure to allergens occurs when internal and mucous membranes are exposed, as with patients who have undergone multiple surgical or invasive procedures (including patients with spina bifida) (3, 4). Latex is presently implicated as a leading cause of intraoperative anaphylaxis, causing up to 19% of such reactions (5, 6). This high prevalence is due in part to the high level of exposure sustained during surgery with latex gloves.

What Is Natural Rubber Latex?

"Latex" is an emulsion of various compounds and does not necessarily imply derivation from the rubber tree. Natural rubber latex (NRL) is a plant product commercially harvested from the Brazilian rubber tree, *Hevea brasiliensis*. It is a complex intracellular product containing the rubber particle cis-1,4 polyisoprene, as well as hundreds of proteins, many of which have been identified as allergens. NRL is usually processed into 2 types of commercial goods: most (90%) is processed into dry sheets (which are converted into molded rubber goods such as tires, shoe soles and vial stoppers), while the remainder is used for dipped rubber products (such as gloves, condoms, and balloons). These dipped products are the chief sources of bioavailable latex allergens (7).

The products which most commonly cause reactions are gloves, balloons and condoms. Gloves and balloons have by far the highest allergen content (Table 2) (8). This is why efforts to limit latex exposure in the medical environment focus on gloves. Although their allergen content is not very high, condoms can cause severe reactions because they come into contact with mucous membranes. Thus, the severity of reaction depends on both the allergen content of the item and its use.

Allergen units (AU) are determined with an ELISA (enzyme-linked immunosorbent assay) method in comparison with a standard preparation (9). The latex allergen content of different products depends largely upon the method of manufacture: dipped products, such as gloves, have a higher protein content than molded products. The proteins are especially concentrated on the surface of the glove, due to vulcanization or curing, which makes the product elastic. Although the amount of allergenic proteins, which are primarily water soluble, can be reduced if gloves are washed and leached, these steps add to the cost of the gloves. Nonsterile examination gloves are generally less "processed" and

TABLE 2
Extractable Latex Allergens in Some Medical and Consumer Rubber Items (6)

Items/Manufacturer	Allergen (AU/mL)
Trojan ribbed condom/Carter Products (New York, NY)	50
Anesthesia breathing circuit Rebreathing bag/Intertech Resources, Inc. (Lincolnshire, IL)	50
Intravenous T-connector/Medex, Inc. (Hilliard, OH)	<5
Nasopharyngeal airway/Porges Corp. (Fairfield, NJ)	<5
Rubber balloon/Betta Products, Inc. (Chatsworth, CA)	4700
Baby pacifier/Playtex Inc., Family Products Div. (Stamford, CT)	<5
EZY infant care ortho nipples/Apothecary Products, Inc. (Minneapolis, MN)	<5
Evenflo wide-base nipples/Evenflo Products Co. (Ravenna, OH)	<5
Bodyguard nonsterile exam gloves/Jason Marketing (Huntington Beach, CA)	2,856–31,673

AU = allergy unit

have a higher protein content than sterile surgical gloves.

The methods used to reduce the "stickiness" of NRL can impact the allergenicity of the product. Powders used to prevent gloves from sticking to the mold ("mold-release compound") such as cornstarch powder, which also aids in the donning and removal of these gloves, can markedly increase direct and indirect exposure to latex allergens through the aerosolization of latex allergens. In contrast, chlorination, a process used to decrease "tackiness," decreases the amount of allergen present.

All of these elements influence the allergenicity of a particular glove or other product. Although the Food and Drug Administration (FDA) Center for Devices and Radiological Health is setting glove standards, there is currently no requirement or regulation for maximum protein or powder content. This creates a product selection quandary when attempting to select products that will effectively reduce latex exposure. Because of this lack of regulation, latex allergen content can fluctuate as much as several thousand-fold, even within the same brand and type, and at different times (10).

Protein and Powder

Latex allergy is an IgE antibody-mediated response to certain proteins present in NRL. Tests are available to measure the amount of total protein present, but they do not distinguish between allergenic and non-allergenic proteins. The modified Lowry assay, which is used most frequently, is relatively inexpensive and simple to perform, but becomes less accurate below protein levels of 50 µg/g. More recently, immunochemical assays have been developed, such as the latex ELISA for antigenic protein (LEAP) and radioallergosorbent test (RAST) assays, which are accurate to much lower levels of allergen and measure allergen as opposed to total protein content. Even though the Lowry method lacks the sensitivity and specificity of immunochemical methods (which are 150 times more sensitive), this assay method has become the current national standard, as ASTM D5712 (11). Many gloves currently on the market are designated "low protein" or have their protein levels printed on the package; however, the FDA does not require such labeling. Moreover, "safe" levels have not been established (12).

Many latex gloves, especially those that are produced cheaply, carry large amounts of powder. While the powder, usually cornstarch, is immunologically innocuous for most people, there is evidence that it contributes to granuloma formation, delayed wound healing, and increased infection rates in some individuals (13). The powder binds with latex proteins and is small enough to be inspired easily (14). As a result, latex proteins are constantly being inhaled in any environment where powdered gloves are in frequent use. The amount of airborne allergen is directly related to the frequency of changes of powdered gloves (15). In addition, the powder carries the proteins into the air and the air circulation systems of buildings as well as onto hair, clothing, charts, etc.

Education regarding gloves is essential. For the protection of their patients and themselves, physicians should insist on powder-free gloves and should be aware of the protein content of the gloves they use. According to the American College of Surgeons (16), "The ideal glove is one with less than 1 microgram/gm of allergen by the LEAP test and one to 14 allergen units/mL on the RAST inhibition assay. One should at least insist the gloves be less than

10 by LEAP assay or less than 100 allergen units on the RAST."

Incidence

Various studies of the incidence of latex allergy have defined it in different ways, and of course the definition will influence the results. Evidence for latex allergy can be elicited by a thorough history, or by RAST, skin prick testing (SPT), or provocation testing. Patients born with spina bifida have the highest prevalence of latex allergy of any known group, with sensitization rates of 30–65% (17). This high rate is probably due to the frequent occurrence of invasive procedures, such as catheterizations with latex catheters, and frequent surgery with latex gloves (4). Multiple reports of perioperative anaphylaxis in these patients in various parts of the country prompted the Centers for Disease Control and Prevention (CDCP) to alert medical personnel to this danger in 1991 (18). Physicians should report all episodes of anaphylaxis during procedures requiring general anesthesia, through their respective state health departments, to the Epidemiology Branch, Hospital Infections Program, in the Center for Disease Control's (CDC's) National Center for Infectious Diseases (telephone 404-639-1550).

The most important common denominator for latex allergy is frequent exposure to latex. Atopic individuals who experience ongoing exposure to NRL are at greater risk for developing latex allergy. Groups at increased risk therefore include patients who have undergone multiple operations and workers, including physicians, nurses, dentists, food service workers, factory workers and day care workers, with occupational exposure to gloves. The incidence of latex allergy among health care workers and individuals with high occupational exposure is 5–17% (19–25).

There are industry-based reports suggesting that NRL exposure does not affect the sensitization rate of latex allergy. These reports are based on analysis of stored sera from phase 1 of the National Health and Nutrition Examination Survey (NHANES III 1988–1991) (26), which were tested for antibodies to latex to estimate the prevalence of latex sensitization in this representative sample of the U.S. population. Because of continuing scientific uncertainty about the results, this analysis has not been published in a peer-reviewed journal; therefore, the CDC warns that these reports should be read with caution. The NHANES survey was not designed to assess latex allergy; therefore, information regarding actual latex exposure of participants was never gathered. Because employment and job title may not indicate the extent of exposure to latex, individuals must be categorized specifically with regard to their exposure. For example, a psychiatrist, with no ongoing latex exposure, is categorized in most studies of prevalence as a health care worker. On the other hand, there was the well-known case of a farmer who developed anaphylaxis intraoperatively and was later shown to have latex allergy. His doctors were baffled until they discovered that he had donned and doffed latex gloves many times a day to protect himself from pesticides.

Presence of latex-specific serum IgE is not synonymous with clinical latex allergy. In most studies, those with clinical latex allergy are a subset of a larger group with latex-specific IgE. It is possible that those with latex-specific IgE who are asymptomatic may progress to symptomatic disease as the result of continued exposure (27). Our experience leads us to agree with the incidence of clinical latex allergy cited by Brown et al. (28) of at least 2% in highly exposed medical personnel. There are about 100 attending anesthesiologists in the Anesthesia Department at Mount Sinai. One of us (BZP) has severe clinical latex allergy and has been unable to work since March 1997. Another staff member has also had to leave the practice of anesthesiology because of latex allergy. A third member of the department has latex allergy, but has been able to continue to work by practicing personal latex avoidance and taking a variety of medications. This individual has never experienced anaphylaxis in response to latex. Several residents in the department either have or suspect that they have latex allergy, but prefer to remain anonymous for fear of jeopardizing their training and future ability to get a job.

Diagnosis

A knowledgeable physician should counsel all individuals with a strong history of latex allergy. Experienced physicians will often perform *in vitro* tests, as well as skin or challenge, testing to confirm the diagnosis. The only FDA-approved test for latex allergy is the RAST. The latex-extract skin prick test (SPT) is considered more sensitive and specific than the RAST; it is not yet FDA approved but appears to be safe and efficacious. Since only one-quarter of patients with a positive skin test are symptomatic, this test must be interpreted with caution (29). If a positive result is associated with a suggestive clinical history, these tests can be considered diagnostic; however, as a screening tool, RAST testing is of uncertain value.

Ideally, conflicting results, either history-positive/test-negative, or history-negative/test-positive, should be confirmed with further studies. A latex glove provocation procedure can be used to confirm sensitivity. The procedure involves pricking the skin on the dorsum of the hand followed by application of a high-allergen glove (30). Wheal and flare at the puncture site are diagnostic. This provocation has also been used in clinical trials of NRL test extracts. Inhalation challenge by qualified personnel with experience in managing anaphylaxis may be used as an alternative for some subjects (31).

In many circumstances, logistical or time constraints prevent extensive evaluation. For history-negative/RAST or skin-test-positive individuals in the occupational setting, it would be prudent to limit direct contact with latex products and to use latex alternatives as appropriate. For patients, a positive latex test must be taken very seriously despite the absence of prior symptoms. There are many examples of anaphylaxis in previously asymptomatic persons who undergo invasive or surgical procedures or even rectal (32) or vaginal (33) examinations. Exposure and reaction to latex via mucosal contact can be many times greater than with occupational or casual exposure.

Further testing (such as skin prick testing or latex glove use tests) must be done for history-positive/RAST-negative persons. Up to 25% of patients with true latex allergy will not have latex-specific serum IgE, but rather cell-bound IgE (34). Furthermore, serum IgE may be transiently cleared from the bloodstream by overwhelming exposure to latex antigen.

In order to make a diagnosis of latex allergy, the only absolute requirement is an index of suspicion. The case of one patient illustrates this point. During the cesarean delivery of the patient's second child 13 years ago, she developed anaphylactic shock about 10 minutes into the surgical procedure. No attention was paid to the fact that four latex-gloved hands had been placed within her abdominal cavity. Anaphylaxis was recognized and treated promptly. Since epidural fentanyl was the only drug the patient had received prior to the event, it was considered to be responsible and was reported as such (35). Subsequently, an allergist familiar with the issue diagnosed latex allergy. A retraction was then published (36). One wonders how many episodes of latex allergy, anaphylaxis, and even death have been wrongly attributed to other causes.

It is vital to be aware that about 50% of latex allergy subjects also have a food hypersensitivity (37, 38). The most common culprits are avocado, banana, kiwi and chestnut, but other foods have been reported as well. If individuals present with anaphylaxis due to these foods, latex allergy must also be suspected.

Management

The cornerstone of latex allergy management is avoidance. Desensitization has not proved successful thus far. Patient education is essential, especially since health care provider education and acceptance of latex allergy is so variable. Excellent professional resources are available on the internet (39) as well as from local and national support groups. Patients must be counseled to wear a medic-alert bracelet, and to carry an epi-pen and other appropriate medications with them at all times. They must be aware of products and environments most likely to trigger reactions and, if necessary, educate their health care providers. Although there are thousands of products that contain NRL, only a small number of them (such as gloves and toy balloons) contain a sufficient allergen load to present an immediate risk to most individuals with latex allergy (8).

Allergen content of items varies greatly. In daily life, balloons present a significant risk (children's birthday parties, department store displays) and must be avoided. Another area of risk is the use of latex gloves in food service (40, 41). Latex gloves are often used when preparing uncooked foods, such as salads. When powdered high-protein gloves are used to toss a damp salad, the allergenic proteins are transferred to the food, and can cause severe reactions in a latex-allergic individual who eats it. However, the most dangerous environments are medical facilities. A visit to the dentist or gynecologist requires foresight and cooperation. The unplanned need to utilize ambulance or emergency room services can be life threatening.

Management of Patients in the Hospital

Many elaborate protocols have been developed to protect patients with diagnosed or suspected latex allergy in the hospital and operating room. These vary in specifics, but all include labeling the patient, labeling the chart, alerting all departments (nursing, dietary, pharmacy, x-ray, housekeeping, etc.), placing the patient in isolation in an area where no latex gloves are used, and scheduling the patient as the first case of the day in the operating room to minimize airborne latex. These protocols also include provision in the hospital of a latex-free cart, and/or a latex-free crash cart. The institution of latex avoidance protocols has reduced the incidence of intraoperative anaphylaxis (42). Unfortunately these protocols, which are baroque in their complexity, may fail to protect the patient fully and can lead to a false sense of security. A colleague with severe latex allergy unknowingly ate an item that had been handled with latex gloves. Driving in his car shortly thereafter, his mouth began to swell; he developed progressive urticaria and bronchospasm, and began to feel some respiratory stridor. He drove to the nearest emergency room and was able to inform them that he was having an allergic reaction to latex. He was placed on a stretcher, and a latex-free cart was wheeled up. Nevertheless, a person attempting to be helpful thought that this patient might soon require intubation and placed a box of powdered latex gloves next to his head. Fortunately, subcutaneous epinephrine, followed by oral medications, relieved his respiratory distress.

Management of Health Care Personnel

Many individuals working in the health care field have the mistaken notion that people with latex allergy can return to the workforce if they are simply provided with non-latex gloves. This wishful thinking is dangerous and can lead to heightened sensitivity and, ultimately, to the loss of a career. Individuals with latex allergy can become exquisitely sensitive to latex proteins that are spread throughout the health care environment. Powder is a major culprit, since it carries latex allergens all over the hospital or other setting. Those who continue to work using non-latex gloves in an otherwise unchanged environment are at high risk to develop occupational asthma, which can have lifelong consequences (43).

With ongoing exposure, individuals may require less and less allergen to cause a reaction, a phenomenon known as priming (44). Another complicating factor is the variability in the amount of latex exposure. An allergic person may seem fine for several days, followed by a day when his rhino-conjunctivitis and asthma are almost uncontrollable. The individual is often puzzled by this symptom variability, and his colleagues may question his veracity. The explanation may lie in large part in the variability of allergen exposure, which depends on factors such as ventilation and glove batch. In addition, an individual's responsiveness to a standardized allergen challenge may vary over time.

Strategies for Combating Latex Allergy

The optimal approach to controlling latex allergy is for an institution to stop using products containing NRL. Some institutions, notably Johns Hopkins, now use non-latex gloves throughout the institution. The benefits should be dramatic, since the allergen contribution of products other than gloves is tiny by comparison. This NRL reduction strategy eliminates the issue of environmental contamination by airborne latex allergens. It also significantly reduces the risk of occupational asthma for those already sensitized. The risk of allergic reactions associated with direct or indirect latex exposure is reduced for everyone in the environment, and there is no need for elaborate protocols to protect patients with latex allergy.

A second approach is to ban all powdered latex products and provide non-latex gloves for those who need them or choose not to expose themselves. This has been termed the "latex-aware" or "latex-reduced" approach, and has been adopted at some institutions, especially those children's medical centers that treat many spina bifida patients (45). At the Mayo Clinic, a multidisciplinary latex-allergy task force recommended that low-allergen gloves be used throughout the institution (46). Despite the concern that lower-allergen gloves would be more expensive, no correlation between glove cost and allergen content was found. Mayo Clinic was able to consolidate purchases and save money.

Another proposal has been the creation of "latex-free" zones within an institution. This shows a fundamental lack of understanding of latex allergy. You cannot quarantine or restrain a protein; it can become airborne and be carried on clothing, hair, and charts. However, in geographically isolated areas of an institution, such as laboratories, this strategy may be of some benefit.

Environmental and product standards have yet to be developed; therefore, it is critical to develop goal-oriented terms and objectives that are practical and clear. "Latex-free" is the term used to describe products that are not manufactured from NRL. "Latex-safe" is the term most often used to describe an environmental and product standard which does not place latex-allergic individuals at risk for allergic reactions and heightened sensitivity, either by direct or indirect (inhalation) latex exposure. In addition, a latex-safe environment is one which reduces the risk of others developing latex allergy by the elimination of significant latex exposure.

Governmental Responses

The only regulatory response to the latex allergy epidemic thus far came in September 1998, when the FDA required labeling of all medical products that contain latex and banned the misleading label "hypoallergenic" (47). The National Institute for Occupational Safety and Health (NIOSH) has made some recommendations regarding latex allergy, including the use of low-allergen, powder-free gloves (48). However, NIOSH is a governmental agency responsible for conducting research and making recommendations for the prevention of work-related illnesses and injuries, but has no regulatory powers. The Occupation Safety and Health Administration (OSHA), which does have such powers, has yet to generate any standards specific to latex exposure (49).

Latex Allergy: The Future

Some latex glove manufacturers have instituted changes in their glove manufacturing process to reduce latex allergen levels. However, there are no government regulations regarding allergen content. Until there are, latex gloves will probably remain a public health problem. Voluntary labeling of gloves with their protein and powder content can help institutions protect their employees by lowering latex allergen exposure. Legal pressures on the rubber industry (litigation from injured or disabled parties) or, to some degree, pressures from the medical profession and advocacy groups, may bring about further improvements.

Many believe that the transition toward a latex-safe environment will be costly. However, a recent analysis of the financial impact, including the potential cost of disability payments, concluded otherwise (50). Two strategies, latex-safe versus status quo, were studied in three health care settings. Even with extremely low rates of latex allergy disability, the move to a latex-safe environment was deemed to be cost-effective. Reduced sick time and enhanced work performance are thought to be additional benefits.

Ultimately, government regulations (and penalties) will probably be necessary to ensure that changes take place. The FDA has had proposed limits on powder and protein on medical gloves in the Federal Register since July 1999 (51), but no regulatory action has been taken to date.

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Comparison of Arterial Systolic Pressure Variation with Other Clinical Parameters to Predict the Response to Fluid Challenges during Cardiac Surgery

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Abstract

Prophylactic optimization of stroke volume during surgery has been thought by some to reduce complications following surgery. Mechanical ventilation has been shown to induce variations in systolic systemic arterial blood pressure. Measuring such variations in systolic pressure (SPV) might serve as an attractive method for guiding fluid therapy intraoperatively. It is unknown if variations in systolic pressure following the rapid intravenous administration of a specific volume of fluid would lead to changes in pressure measurements obtained from a pulmonary artery with sufficient sensitivity to predict or guide the need for expansion of the intravascular volume to optimize stroke volume as an index of cardiac function. The purpose of this study was to determine if such measurements of changes in systolic pressures would be useful in optimizing stroke volume.

Nineteen patients undergoing cardiac surgery were enrolled in a prospective cohort study. Following induction of general anesthesia, one or more 250 mL boluses of 6% hetastarch were administered. Stroke volume was calculated from the cardiac output obtained by thermodilution using a pulmonary artery catheter. If the patient's stroke volume increased by less than 10% as a result of a given fluid challenge, the patient was classified as a non-responder. However, if the stroke volume increased by more than 10%, the patient was classified as a responder. The variations in systolic pressure and echocardiographic indices were simultaneously measured before and after the administration of each 250 mL fluid bolus.

Pulmonary artery occlusion pressure (PAOP) values were significantly lower in patients who responded to fluid boluses ($p=0.0085$) than in those who did not. Similarly SPV and SPV_{down} values (defined as the decrease in systolic pressure with ventilation) were significantly greater in the responders ($p<0.05$). No significant intergroup differences were observed in SPV_{up} (increase in systolic pressure with ventilation) or echocardiographic-derived left ventricular end diastolic area. A PAOP value less than 10 mm Hg predicted a response (sensitivity 68%, specificity 79%). Although significant intergroup differences in the extent of systolic pressure variations were observed, no appropriate threshold values could be determined that would accurately predict the response to a fluid bolus.

There is a relationship between SPV and SPV_{down} values and intravascular volume status. SPV and echocardiographic-derived values did not predict the response to a fluid bolus as well as values obtained from the pulmonary artery catheter.

Key Words: Intravenous fluid administration, hemodynamic monitoring, systolic pressure variation.

Glossary

CABG — coronary artery bypass graft
CO — cardiac output
EDA — end diastolic area (as measured by transesophageal echocardiography)
ESA — end systolic area (as measured by transesophageal echocardiography)
HES — 6% hetastarch in isotonic saline
HR — heart rate, BPM—beats per minute
LVEDA — left ventricular end-diastolic area (from echocardiogram)
MAP — mean arterial systemic pressure
nRES — non-responder; a less than 10% increase in stroke volume as a result of a 250 mL bolus of 6% hetastarch
PAP — pulmonary artery pressure
PAC — pulmonary artery catheter
PAOP — pulmonary artery occlusion pressure
RES — responder; a greater than 10% increase in stroke volume as a result of a 250 mL bolus of 6% hetastarch
SPV — systolic pressure variation
SPV_{down} — the decrease in systolic systemic arterial pressure that results from the decreased left ventricular preload that occurs during positive pressure ventilation
SPV_{up} — the increase in systolic systemic arterial pressure that results from the transient increase in left ventricular preload that occurs during the early phase of positive pressure ventilation
SPV_{total} — the total arterial systolic systemic pressure variation defined as the sum of SPV_{up} and SPV_{down}
SV — stroke volume
TEE — transesophageal echocardiography

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Introduction

MORBIDITY IS COMMON following moderate- and high-risk surgical procedures (1 – 6). Prophylactic optimization of stroke volume (SV) and other indices of oxygen delivery in surgical patients have been demonstrated in some randomized clinical trials to reduce complications and postoperative length of stay (7 – 13). Three randomized clinical trials used the esophageal Doppler to guide the administration of dynamic fluid challenges (7 – 9). The goal of these stroke volume (SV) guided dynamic fluid challenges was to expand the intravascular volume and thereby avoid hypovolemia. Avoidance of hypovolemia was thought to be an attractive method of preventing systemic inflammation attributed to splanchnic mucosal ischemia (1, 3, 5, 14, 15). Routinely used triggers of fluid therapy, e.g., systemic hypotension and tachycardia, are insensitive measures of hypovolemia (1, 16, 17).

Variables that can be used to guide fluid therapy intraoperatively include those obtained via a pulmonary artery catheter (PAC), such as pulmonary artery diastolic and pulmonary artery occlusive pressures (PAOP). Esophageal Doppler and transesophageal echocardiography (TEE) can be used to measure SV and left ventricular end diastolic area respectively.

SPVs are fluctuations in the systolic arterial blood pressure related to mechanical ventilation. During positive-pressure ventilation, upon inspiration, the increase in intrathoracic pressure propels blood out of the lungs into the left atrium and left ventricle and transiently augments left ventricular preload, SV, and systolic arterial blood pressure. The increased intrathoracic pressure results in reduced venous return to the right atrium, which causes decreased left ventricular filling, preload, SV, and systolic arterial blood pressure. Using the systolic arterial blood pressure at the end of expiration as a reference point, the initial increase of systolic arterial blood pressure above baseline during inspiration is called delta up (SPV_{up}), and the subsequent decrease below baseline during inspiration is called delta down (SPV_{down}). The total systolic pressure variation (SPV_{total}) is defined as the sum of SPV_{up} and SPV_{down}.

SPV can be affected by a variety of factors, including intravascular volume status, cardiac function, chest wall compliance, lung compliance, positive end-expiratory pressure (PEEP), and tidal volume. If these variables remain constant, then changes in the intravascular volume status of the subject are thought to result in changes in the SPV (18, 19). Perel et al. demonstrated that SPV and delta down are sensitive indicators of hypovolemia in a dog model (20). Rooke et al. found similar results in eight patients, with SPV and delta down increasing with graded hemorrhage (21). Similar results were reported by Ornstein et al. in 15 patients with good ventricular function undergoing coronary artery bypass graft (CABG) surgery who were subjected to hemorrhage (22).

In contrast to previous studies that focused primarily on the response to graded hemorrhage, none have explored whether the optimization of stroke volume (SV) can be correlated with SPV parameters in patients undergoing coronary artery bypass graft surgery (CABG). Our study sought to determine if SPV-derived parameters accurately predicted SV optimization.

Methods

Patients' Inclusion and Intraoperative Management

The clinical investigations described in this manuscript were conducted in accordance with the guidelines of the Declaration of Helsinki. The study was approved by the institutional review board. Patients younger than 18 years old, and patients with an ejection fraction less than 30% or intracardiac shunts were excluded. After obtaining written informed consent, 19 patients undergoing primary CABG surgery were prospectively enrolled. After catheterization of a radial artery, general anesthesia was induced with fentanyl 10 – 20 µg/kg, etomidate 0.2 –0.3 mg/kg, and pancuronium 0.1 mg/kg. After tracheal intubation, a pulmonary artery catheter was introduced via the right internal jugular vein and a transesophageal echocardiography probe (Acuson, Mountain View, CA) was inserted. A transgastric short axis view of the left ventricle was obtained and maintained for measurements of end systolic (ESA) and end diastolic areas (EDA). Patients were ventilated with tidal volumes of 10 mL/kg, and the respiratory rate was adjusted to maintain P_{aCO2} between 35 and 40 torr. The patient was then positioned for surgical preparation; however, skin incision did not commence until the conclusion of the study protocol.

Heart rate (HR), mean systemic arterial pressure (MAP), pulmonary artery pressure (PAP), PAOP, intermittent cardiac output (CO) obtained by thermodilution, ESA, and EDA were recorded. SVs were calculated on line by dividing the CO by HR. All arterial pressure pulse tracings were obtained during a 15-second period of patient apnea followed by five cycles of controlled ventilation. Arterial pressure pulse tracings were analyzed later to determine the extent of SPVs.

After obtaining the aforementioned initial hemodynamic data, 250 mL of normothermic 6% hetastarch in normal saline (HES) was administered via an indwelling intravenous catheter within approximately 5 minutes. Measurements of hemodynamic data were repeated 5 minutes after the conclusion of the fluid bolus. If the patient's SV increased by less than 10%, the patient was classified as a non-responder (nRES) to that bolus of fluid, and the protocol was terminated. If the patient's SV increased by 10% or more, the patient was classified as a responder (RES). In these responding patients, a second 250 mL bolus of HES was then administered, and the hemodynamic measurements were repeated. If the SV now increased by 10% or less, the patient was then classified as a non-responder (nRES) and the protocol was terminated. If, however, the SV increased by 10% or more, the patient was classified as a responder (RES). In this situation, the fluid bolus was repeated for a third and final time during which time the same hemodynamic measurements were repeated. Once again, the patient was classified either as a RES or a nRES. The interval between the start of each fluid bolus was 10 minutes.

SPV Calculations

All SPV calculations were performed "offline" after completion of the study protocol. A systolic systemic arterial pressure was measured during the last five seconds of patient apnea. This measurement served as the baseline from which SPV_{up} and SPV_{down} were calculated. The maximal increase in systolic systemic arterial blood pressure during early inspiration above the apneic systolic pressure was defined as SPV_{up}. The difference between the systolic systemic arterial blood pressure and the maximal decrease in systolic pressure during positive pressure ventilation was defined as SPV_{down}. The sum of SPV_{up} and SPV_{down} was defined as SPV_{total}.

Statistical Analysis

The goal of the present study was to determine whether SPVs accurately reflected changes in SV. Hence, each fluid bolus was considered a separate case and assumed statistical independence. Differences in SPV_{up}, SPV_{down}, SPV_{total}, EDA, and PAOP between RES and nRES groups were analyzed by the Student's t-tests. Differences in hemodynamic parameters between sequential boluses were analyzed by paired Student's t-tests with correction for multiple comparisons. All analyses were two tailed, and a p value ≤ 0.05 was considered significant.

Results

Demographic data for the 19 patients who were studied are summarized in Table 1. Patients received a total of 36 boluses of HES. Six patients received only 1 fluid bolus (total 250 mL), 9 patients received 2 boluses (total 500 mL), and 4 patients received 3 boluses (750 mL total). Hemodynamic data during pre-bolus conditions and subsequent fluid boluses are summarized in Table 2. In response to the first fluid bolus, there was a statistically significant increase in systolic and diastolic pulmonary artery pressures, PAOP, CO, and SV as well as a significant decrease in SPV and SPV_{down} comparing these values before vs. after the first fluid bolus. There was a significant increase in pulmonary artery diastolic pressures and PAOP while SPV and SPV_{down} decreased in response to the second fluid bolus, while no significant differences were detected in any of these responses to the third fluid bolus.

Only 4 out of the 19 patients met the protocol to receive a third bolus of 250 mL of fluid (total 750 mL). The SVs of these four patients at the 4 time points were: 55/63/68/63; 42/55/69/73; 33/40/47/48; and 35/53/60/63. Only the first of these patients demonstrated a decrease in the SV in response to the third fluid bolus.

The 36 cases of fluid boluses were characterized as RES (n=17) (SV increased by 10% or more) or nRES (n=19) (SV increased by less than 10%). Variables relating to intravascular fluid volume that were assessed in our study, divided into RES versus nRES, are summarized in Table 3. PAOP values were significantly lower in patients who responded to fluid boluses (p=0.0085) compared with those who did not. Similarly SPV and SPV_{down} values were significantly greater in

TABLE 1

Demographic Data of 19 Patients

Age (years)	63 ± 9
Weight (kg)	83 ± 15
Height (cm)	172 ± 9
Number of vascular grafts	median 3 (range 2–5)
History of hypertension	8/19
History of diabetes mellitus	10/19
History of chronic renal insufficiency	1/19

Mean ± SD except where noted

TABLE 2
Hemodynamic Data Summary

	Baseline (n = 19)	250 mL (n = 19)	500 mL (n = 13)	750 mL (n = 4)
HR BPM	63 ± 12	62 ± 12	62 ± 11	64 ± 7
MAP mm Hg	74 ± 10	79 ± 12	83 ± 12	85 ± 11
Systolic PAP mm Hg	28 ± 8**	32 ± 9	32 ± 7	32 ± 6
Diastolic PAP mm Hg	12 ± 6**	15 ± 6++	15 ± 5	20 ± 6
PAOP mm Hg	10 ± 5**	14 ± 7++	15 ± 4	20 ± 9
CO L/min	4.2 ± 1.8**	4.8 ± 1.9	5.1 ± 2.1	3.9 ± 0.7
SV mL	64 ± 18**	77 ± 22	81 ± 21	62 ± 10
LVEDA cm^2	17.3 ± 6.9	18.6 ± 6.5	20.2 ± 7.1	21.0 ± 6.0
SPV mm Hg	7.2 ± 4.3**	5.2 ± 2.9+	4.9 ± 2.6	3.3 ± 1.3
SPV$_{up}$ mm Hg	2.6 ± 1.4	2.6 ± 0.9	2.9 ± 1.0	2.2 ± 1.0
SPV$_{down}$ mm Hg	4.6 ± 4.1**	2.6 ± 3.0+	2.1 ± 2.5	1.1 ± 1.1

Table columns represent cumulative volume of fluid boluses.
For abbreviations — see glossary
* $p<0.05$ after first fluid bolus
** $p<0.01$ after first fluid bolus
+ $p<0.05$ after second fluid bolus
++ $p<0.01$ after second fluid bolus

the RES group ($p<0.05$). No significant difference between groups was observed with regard to LVEDA or SPV$_{up}$ values. An initial pulmonary capillary wedge pressure value of less than 10 mm Hg was the optimal predictor of responders with a sensitivity of 68% and a specificity of 79%. Although SPV and SPV$_{down}$ values (as a continuous variable) were predictive of likelihood of response to fluid challenge, when comparing RES versus nRES, no appropriate threshold values of either variable could be determined to accurately predict the response to a fluid bolus.

Discussion

Recent studies suggest that occult hypovolemia and hypoperfusion in the perioperative setting may be an avoidable cause of postoperative morbidity (7–13). These studies all had the same overall goal of avoiding occult hypoperfusion. Some of the investigators employed a protocol involving the administration only of fluids (7–9), whereas others employed both fluids and inotropic agents (10–13).

There is no easy way to accurately and quickly measure and monitor changes in intravascular volume. One limitation of our study is that we assumed the PAC to be a "gold standard" for guiding fluid therapy. Clearly, PAOP and PAD are imperfect measures of intravascular volume status. Compensatory arterial and venoconstriction can result in cardiac filling pressures that appear normal despite significant hypovolemia (16, 26).

TABLE 3
Presumptive Indicators of Patient Optimization

	RES (n = 17)	nRES (n = 19)	p value
PCWP mm Hg	9 ± 4	13 ± 4	0.0085
LVEDA cm^2	16.7 ± 5.8	19.0 ± 6.8	NS
SPV mm Hg	8.2 ± 3.9	5.3 ± 2.6	0.0179
SPV$_{up}$ mm Hg	2.8 ± 1.5	2.6 ± 1.0	NS
SPV$_{down}$ mm Hg	5.4 ± 3.9	2.7 ± 2.8	0.0246

Since each fluid bolus was considered a separate case and assumed statistical independence, all boluses are presented as aggregate data.
p values of differences between RES and nRES groups; NS = not significant.

Use of SPV or SPV$_{down}$ values could theoretically be used to enhance stroke volume and cardiac performance. Our data demonstrate that changes occurred in SPV and SPV$_{down}$ values in relation to the intravascular volume status prior to a fluid bolus. In contrast, we found no relationship between echocardiographic-derived parameters (e.g., left ventricular end diastolic area) and intravascular volume status. SPV parameters, however, were poorer predictors of the need for additional fluid than were measurements derived from the PAC. Although esophageal Doppler-guided fluid administration has suggested improved outcome in several clinical studies (7–9), it is not known whether such measurements would better correlate with directly measured SV.

Another limitation of our study is that we measured SPV parameters off line. To be clinically useful, however, a manufacturer of monitoring equipment would need to create an algorithm that provides for real time assessments of SPV and SPV_{down}. This yet to be determined algorithm would ideally detect pulmonary airway pressures and tidal volumes so as to most accurately assess SPV parameters.

Patients excluded from participating in the study, e.g., those younger than 18 years old, and patients with a left ventricular ejection fraction less than 30% or intracardiac shunts, represent another limitation to our study. Yet most patients undergoing cardiac surgery are older than 18 years, do not have intracardiac shunts, and have a left ventricular ejection fraction greater than 30%. Hence, exclusion of these patients does not significantly limit our ability to generalize our results to most adult patients undergoing cardiac surgery.

Summary

In summary, we demonstrated a significant difference in some SPV parameters in patients in whom SV could be increased by the relatively rapid administration of additional fluid. Although significant differences were observed, no threshold values of these SPV parameters could reliably predict, in patients undergoing elective cardiac surgery, the amount of the additional volume to be administered. PAC-derived values best predicted the response to a fluid bolus.

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Preemptive Epidural Analgesia for Thoracic Surgery

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Abstract

The purpose of this study was to determine if preemptive epidural analgesia performed before thoracotomy incision and during the operation reduces postoperative pain. Patients in the treatment group received 8 mL of 0.25% bupivacaine and 2 mL of fentanyl (50 μg/mL) via the epidural route prior to skin incision, followed by an infusion of bupivacaine 0.1% and fentanyl 10 μg/mL at 6 mL/hr. The control group received saline in the epidural. All patients in both groups were dosed with 8 mL of 0.25% bupivacaine and 2 mL of fentanyl 50 μg/mL via the epidural route at the time of the chest closure. The patients in the treatment group required less isoflurane intraoperatively and had lower maximum pain scores in the first 6 hours postoperatively. No significant differences were noted after the first 6 hours.

Key Words: Preemptive analgesia, epidural analgesia, thoracic surgery.

Introduction

THORACOTOMY OFTEN LEADS TO significant pain postoperatively. There may also be pulmonary dysfunction, which can be due to the removal of lung tissue, poor preoperative lung function, splinting from pain, and respiratory depression from parenteral narcotics (1 – 3). The pain may reduce the ability to take deep breaths and cough. Intravenous narcotics may depress respiration and also produce side effects such as nausea and vomiting. Epidural analgesia or intrathecal morphine is often used for treatment of post-thoracotomy pain, and reduces the need for systemic narcotics.

There is some evidence that tissue injury leads to nervous system changes that create hypersensitivity to pain postoperatively. This hypersensitivity is thought to be due to a lower threshold to pain in the peripheral nociceptors and an increased excitability of neurons in the spinal cord. There are few data available regarding the use of preemptive analgesia for thoracic surgery. In one report, the administration of fentanyl into the epidural space prior to thoracotomy incision led to reduced postoperative pain and morphine requirements, compared with patients who received the same dose of epidural fentanyl 15 minutes after skin incision (4). However, no additional analgesics were administered during the surgery, and local anesthetics were not utilized for treatment. The purpose of the present study was to determine if preemptive epidural analgesia that was provided before thoracotomy incision and intra-operatively reduces postoperative pain and postoperative narcotic usage.

Methods

The protocol was approved by the Institutional Review Board, and written informed consent was obtained from all 40 patients who were studied. These patients were scheduled to undergo elective thoracic surgery (thoracotomy, or thoracoscopy with possible thoracotomy). All patients included in the study had a thoracic epidural catheter placed while in the preoperative holding area. A test dose of 3 mL of bupivacaine 0.25% was administered via all of the epidural catheters immediately following placement.

The study was conducted in a double-blind fashion. Patients were assigned to one of two groups, according to a list of random numbers. In Group A, 8 mL of bupivacaine 0.25% and 2 mL of fentanyl (50 μg/mL) were injected into the epidural catheter after induction of general anesthesia and before skin incision. This was followed by an epidural infusion of bupivacaine 0.1% and fentanyl 10 μg/mL at 6 mL/hr that

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was continued throughout the procedure until chest closure was performed.

In Group B, 10 mL of preservative-free normal saline was injected in the epidural catheter after induction of general anesthesia and before skin incision. This was followed by an epidural infusion of normal saline at 6 mL/hr that was continued throughout the procedure until the chest closure.

Intraoperatively, all patients received oxygen, isoflurane, neuromuscular blockers, and a maximum total fentanyl dose of 3 µg/kg intravenously. At the beginning of the chest closure, all patients in both groups received 8 mL of bupivacaine 0.25% and 2 mL of fentanyl (50 µg/mL) through the epidural catheter. Patients were continued in the study protocol only if a thoracotomy incision was performed.

At the conclusion of surgery, patients were extubated if clinical criteria were satisfied. Otherwise, patients were transferred to the Post-Anesthesia Care Unit (PACU) still intubated, and were extubated later when extubation criteria were met. Upon each patient's arrival at the PACU, an epidural infusion of bupivacaine 0.1% with fentanyl 10 µg/mL was begun at 2 mL/hr. This infusion was titrated according to the clinical needs of each patient. The patients graded their pain on a linear analog scale (Visual Analogue Scale — VAS) of 1 – 10 for 48 hours postoperatively, on an hourly basis while awake. The rate of the epidural infusion was recorded.

The data were analyzed using unpaired Student's t-tests. A $p<0.05$ was considered statistically significant.

Results

Thirty-two of the 40 patients initially enrolled in the study underwent a thoracotomy incision, and all of these patients completed the study. The demographic data of patients were similar in both groups. The results are summarized in Table 1.

The patients in Group A had a lower intraoperative requirement for isoflurane, compared with Group B (0.5 ± 0.5% vs. 0.78 ± 0.2%, respectively, $p<0.05$). The intraoperative hemodynamics were similar in both groups (Table 1).

Postoperatively, the patients in group A had a lower maximum pain score in the first 6 hours compared with group B; the pain scores were not significantly different after the first 6 hours (Table 2).

TABLE 1
Intraoperative Data

	Preemptive Analgesia	Control	P-value
n	19	13	
Mean end-tidal isoflurane (intraop) (%)	0.5 ± 0.15	0.71 ± 0.23	0.012
Median HR (intraop) (bpm)	74 ± 13	75 ± 5	NS
Median MAP (intraop) (mm Hg)	82 ± 8	88 ± 9	NS

Discussion

In the current randomized, double-blinded, placebo-controlled study, the patients in the treatment group had lower pain scores in the initial 6 hours, but not thereafter. Additionally, the intraoperative requirements for isoflurane were reduced in the treatment group.

Noxious stimuli may induce changes in the central nervous system, even after the original inciting event has ceased (4). Data from animal experiments have demonstrated that these neuroplastic changes can be prevented by pretreatment with analgesics prior to the injury (5, 6). Preemptive treatment with local anesthetics or opioids has been shown in some an-

TABLE 2
Postoperative Data

	Preemptive Analgesia	Control	P-value
Median epidural infusion rate (mL/hr)	4.1 ± 1.5	4.3 ± 1	NS
Maximum pain score (0 – 6 hrs, VAS)	4.1 ± 3.0	6.8 ± 3.6	0.009
Maximum pain score (7 – 12 hrs, VAS)	3.0 ± 2.3	4.5 ± 3.8	NS
Maximum pain score (13 – 24 hrs, VAS)	4.5 ± 2.8	4.2 ± 3.4	NS
Maximum pain score (25 – 48 hrs, VAS)	2.5 ± 1.7	4.5 ± 3.8	NS

VAS = Visual Analogue Scale.

imal studies to be more effective than treatment following injury (6, 7). The existence of phantom limb pain following amputations also supports the theory of central nervous system neuroplasticity.

Tverskoy et al. (8) demonstrated a preemptive effect of both fentanyl and ketamine on postoperative pain and wound hyperalgesia. Patients in the fentanyl group or ketamine group had lower pain scores and higher pain thresholds than patients in the control group, at both 24 and 48 hours postoperatively. In another study, the administration of morphine and ketamine was more effective in treatment of postoperative pain when given preoperatively rather than intraoperatively (9).

Regional anesthesia can also be used to prevent the sensation of noxious surgical stimuli from reaching the spinal cord and leading to neuroplastic changes. Spinal anesthesia for lower abdominal surgery has been reported to lead to less postoperative pain and lower postoperative morphine usage, compared with patients receiving general anesthesia (10).

There are also data that do not support the effectiveness of preemptive analgesia. Johansson et al. (11) reported that preoperative local anesthesia infiltration with ropivacaine for postoperative pain relief after cholecystectomy did not have a prolonged postoperative analgesic effect.

Aida et al. (12) reported that the combination of epidural morphine and intravenous ketamine, administered prior to skin incision for gastrectomy and maintained continuously throughout surgery, produced a preemptive analgesic effect that was still present 48 hours after surgery. In another study, a single dose of ketamine 0.4 mg/kg, administered intravenously prior to skin incision for abdominal hysterectomy, did not have a preemptive analgesic effect (13). Preoperative ketamine did not have a preemptive analgesic effect in patients undergoing total mastectomy (14). The effectiveness of preemptive analgesia may also be affected by the presence of preoperative pain (15) or the type of surgery (16).

Local infiltration of 0.5% bupivacaine prior to incision for laparoscopy resulted in less postoperative pain than either infiltration just prior to skin closure or infiltration of only saline (17). Pre-incisional infiltration of bupivacaine also reduced postoperative pain following lower abdominal surgery conducted under epidural anesthesia (18).

Acute postoperative pain may have long-term implications. Early postoperative pain following thoracic surgery has been reported to be associated with long-term pain 1.5 years postoperatively (19).

In our study, the pain scores differed only during the first 6 hours. This could have been due to a preemptive analgesic effect, but if so, it did not carry forward beyond this initial period. The early reduction in pain in group A could have been due to a better analgesic effect or from using a different dosing technique. These patients had an initial loading dose, followed by an infusion, and then a dose at the conclusion of surgery. The only intraoperative dose that the control group received was at the conclusion of surgery. Group A received a greater amount of local anesthetic and also had lower intraoperative anesthetic requirements, an effect that we had also reported in an earlier study with intrathecal morphine (20).

In conclusion, while there was a beneficial effect of reduced intraoperative anesthetic requirements, any lasting effect of preemptive analgesia did not extend beyond 6 hours after the operation.

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Rofecoxib-Associated Upper Gastrointestinal Bleed:

A Case Report

Gordon M. Freedman, M.D.[1], Joel M. Kreitzer, M.D.[2], and Ruchi Badola, M.D.[3]

Abstract

To our knowledge, this is the first clinical report of a rofecoxib-associated upper gastrointestinal hemorrhage. We urge caution in prescribing rofecoxib to patients with risk factors for peptic ulcer disease and recommend limiting the dose to 25 mg per day for these patients.

Key Words: Rofecoxib, cyclo-oxygenase-2 inhibitor, nonsteroidal anti-inflammatory drug, peptic ulceration, upper gastrointestinal bleed.

Introduction

GASTROINTESTINAL (GI) MORBIDITY is a major complication associated with the use of nonspecific cyclo-oxygenase (COX)-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs). In the US there are 20,000 hospitalizations and 2,600 deaths reported per year. The risk of hospitalization and mortality for GI complications is about 1 – 1.5% and 0.13% per year respectively (1, 2).

COX activation results in prostaglandin production, which mediates important physiological functions. NSAIDs attenuate prostaglandin synthesis by nonspecifically inhibiting COX activity (3). While this nonspecific inhibition attenuates the prostaglandin-mediated peripheral nociceptor sensitization, there is a high incidence of gastrointestinal (GI) complications.

Two isoforms of COX have been identified, COX-1 and COX-2. COX-1 is a constitutive enzyme, primarily responsible for the production of prostaglandins that regulate many physiologic processes, including gastrocytoprotection (4). COX-2 is an enzyme induced by inflammatory stimuli and results in the production of prostaglandins that mediate the inflammatory response and sensitize peripheral nociceptors (5). The new class of NSAIDs, COX-2 specific inhibitors such as rofecoxib, exhibit minimal COX-1 inhibition. Theoretically, selective COX-2 inhibition leads to analgesia and anti-inflammatory effects, while minimizing GI complications. We present a case of a rofecoxib-associated upper GI bleed.

Case Report

The patient is a 48-year-old male with a history of rheumatoid arthritis and Crohn's disease. He had been treated intermittently for fifteen years with prednisone for his Crohn's disease; the last treatment was approximately one year ago. The patient's medical history was significant for peptic ulcer disease diagnosed six years prior to presentation. Esophago-gastroduodenoscopy (EGD) and cultures for *Helicobacter pylori* were negative one year ago. The patient reported no tobacco, alcohol or recreational drug use. His daily medications included omeprazole, clonazepam, and 8 tablets of oxycodone 4.5 mg/aspirin 325 mg for the past fifteen years for pain relief from his Crohn's disease and rheumatoid arthritis.

One month prior to his most recent hospitalization, the patient presented with an exacerbation of his rheumatoid arthritis. The patient started to take rofecoxib 25 mg once daily, but the dose was increased to 25 mg twice daily by his rheumatologist in order to optimize analgesia and further decrease inflammation. Six days later, the patient experienced abdominal pain and vomited "coffee ground" material. Rofecoxib and oxycodone/aspirin were discontinued. An EGD revealed a peptic ulcer of the gastric antrum. The patient's abdominal pain and GI bleeding resolved with conservative management. To relieve his chronic pain, oxycodone 5

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mg every 4 hours was recommended when required. After discharge from the hospital, the patient began to self-medicate with aspirin 325 mg per day. After he consulted with his gastroenterologist, rofecoxib was discontinued and oxycodone/aspirin therapy was restarted, because of the patient's insistence that this combination was the only means of relieving his chronic pain. Since the above incident, the patient has had good pain control and no further GI distress.

Discussion

Rofecoxib, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone, inhibits COX-2 800 times more than COX-1 *in vitro*. *In vivo*, rofecoxib shows dose-related inhibition of COX-2 but no significant COX-1 inhibitory action (6). This selectivity maintains the beneficial effects of COX-1 on the gastrointestinal tract, i.e., increased gastric blood flow, decreased acid secretion and increased gastric mucus secretion, while inhibiting the COX-2 effects of inflammation and pain.

The most commonly reported GI symptoms of patients receiving rofecoxib included epigastric discomfort, diarrhea, and nausea (7). Based upon studies of 1,516 patients, the six-month cumulative incidence of gastroduodenal ulcers in patients taking rofecoxib 25 mg daily was 4.3%; the incidence was 7.5% with rofecoxib 50 mg daily, 25.7% with ibuprofen 2400 mg daily, and 4.7% with placebo (8, 9). These endoscopic studies included patients who were older than 65 years, and patients with a history of GI bleeding, perforation, ulcer, baseline gastroduodenal erosions and active *Helicobacter pylori* infection. These patients had no evidence of active gastroduodenal ulcer at the commencement of the respective studies. Neither study included patients on aspirin-containing medications.

The incidence of GI bleeding with rofecoxib may be lower than the incidence of peptic ulceration in the general population. A study looking at the geometric mean amount of daily fecal red blood cell (RBC) loss in healthy volunteers showed rofecoxib to cause a similar amount of RBC loss compared with placebo, and approximately half the volume of RBC loss relative to the nonspecific COX inhibitor, ibuprofen (10). Among 3,357 patients studied for up to one year and treated with varying daily doses of rofecoxib of up to 50 mg, there were 19 cases of peptic ulcer bleeding, only 3 of which were considered serious upper GI events, using protocol-derived criteria, for a cumulative incidence of 0.09% (11).

To our knowledge, our case report is the first reported description of a GI bleed associated with rofecoxib use. The selective inhibition of COX-2 makes this class of medications inherently much safer than the traditional nonspecific NSAIDs. However, as noted in the above discussion of endoscopic studies, the incidence of gastroduodenal ulcers in patients taking rofecoxib 50 mg daily is greater than with placebo, albeit much less than with nonspecific COX-inhibiting NSAIDs. With this in mind, our case report emphasizes the need for caution in prescribing rofecoxib to patients who have had active peptic ulcer disease at one time or another, or a history suggestive of peptic ulcer disease in association with previous use of steroids or NSAIDs. Also, it is our opinion that the daily dose of rofecoxib probably should not exceed 25 mg in a patient at risk for GI ulcer disease. Further studies are needed to determine the safe daily dose range for rofecoxib and to elucidate the relationship between predisposing ulcerogenic factors and rofecoxib-induced GI pathology.

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Cervical Radicular Pain Caused by Herpes Simplex Virus-Type 1 Infection:

A Case Report

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Abstract

A case of a 16-year-old with herpes simplex virus type-1 infection with radicular arm pain is reported. The clinical implications of the case are discussed.

Key Words: Herpes simplex, radiculitis, pain, diagnosis.

Case Report

A 16-year-old white male with a 5-year history of ulcerative colitis developed fever, oral ulcers, and vesicles on his thumbs. Viral cultures of the oral ulcer scrapings revealed herpes simplex virus type-1 (HSV-1), and serology testing was positive for an acute HSV-1 infection. He was treated with a three-day course of intravenous acyclovir; during this time his symptoms resolved. Oral acyclovir was continued for approximately four weeks. A few days after discontinuing acyclovir, he developed herpetic whitlow on his thumbs and was restarted on acyclovir. The vesicles were painful, and over the next three days pain developed in both upper extremities. A pain management specialist near his home treated him for cervical radiculopathy with gabapentin 300 mg and meperidine 50 mg each three times daily and continued the acyclovir. Since this new onset neuropathy was not associated with his prior HSV-1 infection, he underwent two cervical epidural steroid injections, without relief of his pain. He was referred to us for further evaluation. At this time he complained of severe bilateral pain radiating from his fingers into his neck, in approximately the C5–C6 distribution. On physical examination, he had severe allodynia throughout his hands and arms. Motor and sensory functions of the upper extremities appeared normal. No lesions or vesicles were noted; however, he had some mild scarring near the nailbeds of both thumbs. A magnetic resonance imaging (MRI) study of the cervical spine was negative. A diagnostic stellate ganglion block was performed, to rule out a sympathetically mediated pain syndrome, and his anti-viral medication was changed to famciclovir.

Our working diagnosis was neuropathic pain due to HSV-1. The patient was treated with oral methadone, amitriptyline, methylphenidate, and acupuncture. This regimen provided excellent pain relief without side effects. Two months after treatment began, he noted a significant decrease in his pain. Methadone was discontinued. Six months later he was pain free, taking only amitriptyline at bedtime.

Discussion

Common causes of cervical and lumbar radicular pain include spinal disc disease, spinal stenosis, facet disease, and myofascial syndromes; less common etiologies include malignancies, infections, and neuropathies. Radiological imaging, electromyographic (EMG) testing, and the use of diagnostic and therapeutic nerve blocks are often used to diagnose and treat these processes.

Herpes simplex viruses are double-stranded DNA viruses that may occasionally cause cen-

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tral nervous system pathology, most often presenting as acute encephalitis. HSV infections have also been implicated in nervous system symptoms, including numbness and tingling of the buttocks and perineal region, urinary retention and impotence (1). HSV infections have also been associated with peripheral nervous system involvement, such as Bell's palsy and facial neuralgias (2, 3).

Although not often recognized, HSV infection may be the cause of both cervical and lumbar radicular pain. Morris and Peters reported a case of repeated episodes of lumbar radiculopathy associated with outbreaks of HSV (4). Jain reported the cases of two patients with leg pain associated with HSV infection; one of the two underwent lumbar surgery for pain relief (5). Morrison et al. described a patient with complaints of lumbar radiculopathy who underwent an L5–S1 laminectomy and discectomy without change in symptoms (6). This patient eventually developed radicular right arm symptoms, and cerebrospinal fluid samples were positive for HSV-1.

While radicular symptoms from HSV infections have been reported in the literature, they have usually been associated with HSV-2 infections or recurrent HSV infections (5, 7). Belec and Vidailhet reported the case of a patient with monthly outbreaks of herpetic whitlow from HSV-2 infections, who developed repeated episodes of cervical radiculopathy (8). The most recent report of HSV radiculopathy was notable for diffuse neurologic symptoms, including motor and sensory loss in the lower extremities, gait disturbance, sensory ataxia and stool and urinary incontinence (9). In that case, an MRI demonstrated swelling of the dorsal cauda equina fibers.

To our knowledge, this is the first reported case of an acute HSV-1 infection causing cervical radicular pain without any other central or peripheral nervous system symptoms. In the original work-up of the patient's pain, neuralgia from an HSV-1 infection was never considered, and several unnecessary and ineffective invasive procedures were performed for pain relief. This is reminiscent of earlier reports of patients undergoing surgery to obtain pain relief from radicular pain caused by HSV (6, 7).

Considering the frequency of HSV-1 infections, it is important to recognize this viral infection as a possible cause of cervical as well as lumbar radiculopathy. A thorough and precise pain history may help assure proper diagnosis. Radicular pain from structural spine pathology (i.e., disc disease, stenosis) is usually described as radiating from the spine in a distal distribution down the extremity. Upward radiating pain argues against a spinal origin of pain. Our patient described pain radiating upwards from his thumb to his neck. Jain (5) reported a case of leg pain, presumably from HSV, as pain radiating upward from the left big toe, and more recently, Kuker et al. (9) described ascending numbness in a patient with HSV-1 lumbo-sacral radiculopathy.

A review of recent textbooks on pain management (10), back pain (11) and neck pain (12) was notable for the omission of HSV as a possible cause of radicular pain. Since the treatment of HSV radiculopathy requires concurrent treatment of infection and pain with anti-viral agents and analgesics respectively, it is important to consider this possible etiology of radiculopathy and avoid unnecessary invasive procedures.

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Subarachnoid Hemorrhage Presenting as Post-dural Puncture Headache:

A Case Report

Jason B. Wells, M.D.[1], and Ian H. Sampson, M.D.[2]

Abstract

A case of subarachnoid hemorrhage following spinal anesthesia for prostate radioactive seed implantation is reported. The implications of the differential diagnosis of post-dural puncture headache are discussed.

Key Words: Spinal anesthesia, cerebral aneurysm, anesthetic complications, post-dural puncture headache.

Post-dural puncture headache (PDPH) is one of the most common complications of spinal or epidural anesthesia (1). Caused by leakage of cerebrospinal fluid (CSF) from the dural puncture site and the resultant stretching of intracranial dural veins brought about by the associated pressure gradient shift, the headache is typically self-limiting and without sequelae.

Intracranial bleeding is a much rarer, but decidedly more serious complication of spinal or epidural anesthesia. There are few reports on it in the literature; most of them describe subdural hematoma formation (2–6). The mechanism is characterized as an extension of post-dural puncture headache: if the CSF pressure gradient after dural puncture is great enough, stretched dural veins can tear and create a subdural hematoma (2). When post-spinal or post-epidural bleeding occurs in the subarachnoid space, it is typically limited to the spinal levels surrounding the dural puncture site (7, 8). This is in contrast to intracranial subarachnoid hemorrhage (SAH) following spinal or epidural anesthesia, which is extremely rare (9). Such a complication is easily misdiagnosed, because the severe headache of subarachnoid hemorrhage may be mistaken for the more common post-dural puncture headache. We describe a case of postoperative SAH presenting as PDPH in a patient with previously undiagnosed intracerebral aneurysms.

Case Report

A 59-year-old man with prostate cancer presented for implantation of radioactive seeds to the prostate, on an ambulatory basis. His medical history was remarkable for hypertension and hypothyroidism. Medications included enteric-coated aspirin 325 mg PO qd (stopped 15 days prior to surgery), amlodipine 10 mg PO qd, propranolol 80 mg PO tid, levothyroxine 100 µg PO qd, liothyronine 25 µg PO qd, flutamide 250 mg PO tid, and amoxicillin/clavulanate 875 mg PO bid. The patient denied a history of back problems or bleeding diathesis. Preoperative laboratory results included an international normalized ratio (INR) of 0.9, activated partial thromboplastin time (aPTT) of 28 sec, and platelet count of 209,000/µL. While he had no history of spinal or epidural anesthesia, he had undergone general anesthesia in the past without complications. After prehydration with 1000 mL of Plasma-Lyte A® (Baxter Healthcare Corp., Deerfield, IL) and premedication with midazolam 2 mg i.v., spinal anesthesia was performed via a midline approach, with the patient sitting. Landmarks were easily palpated and a single puncture produced clear CSF. A hyperbaric solution of 2 mL 0.75% bupivacaine with dextrose was injected at the lumbar 3–4 interspace using a 27-gauge Whitacre spinal needle via an 18-gauge introducer. A satisfactory level of anesthesia was obtained to T10 and the surgical procedure was completed without incident. Blood pressure, 160/80 mm Hg upon the patient's arrival at the hospital earlier in the day, ranged from 180–190/80–85 mm Hg in the operating room for the several minutes preceding placement of

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the spinal, then quickly settled to a steady 110 – 120/70 mm Hg for the duration of the procedure. The patient remained comfortable and lucid and continued to communicate with the anesthesiologists throughout the procedure.

After an uneventful postoperative course in the post-anesthesia care unit, the patient was discharged home; he was awake, alert, and ambulating. On routine telephone follow-up the next day, the patient's family reported that he was experiencing a headache unresponsive to acetaminophen. While the headache was more intense with the patient sitting or standing, it did not completely resolve when he lay flat. A subsequent telephone contact later in the day found the patient's headache to be improving. He remained alert and coherent until the early morning of the second postoperative day, when he was found by his family to be confused and not fully alert, and was brought to the hospital. On arrival at the emergency department, the patient was somnolent but arousable, with a pulse rate of 85 bpm and a blood pressure of 182/114 mm Hg. A computed tomography (CT) scan of the head and a subsequent cerebral angiogram revealed a subarachnoid hemorrhage and three intracerebral aneurysms — bilateral pericallosal and left middle cerebral artery. The acute bleed was thought to have occurred at the left pericallosal site. Emergency craniotomy was performed, and the three aneurysms were clipped successfully. After effective medical treatment of symptomatic vasospasm in the first postoperative week, the patient was discharged to a rehabilitation facility with resolving unilateral motor weakness.

Discussion

Bottiger and Diezel described a similar incident of post-dural puncture SAH in a patient with a preexisting cerebral aneurysm (9). The authors theorized a mechanism of transmural stress from the CSF pressure gradient, resulting in the rupture of vulnerable aneurysms. Whether the subarachnoid hemorrhage suffered by our patient can be attributed to this mechanism or was related to possible postoperative hypertension following discharge to home, remains unclear. In either case, it is instructive to highlight the differences in presentation between PDPH and SAH, given the potential ease with which the more serious of the two can initially be masked.

PDPH is classically characterized as a positional headache that starts at the top of the head or the occiput and extends down the back of the neck. The headache may rarely occur at the time of dural puncture or, conversely, several days or even weeks afterwards, but is most commonly reported to commence on the day following the procedure. Patients typically report that the pain, while not responsive to acetaminophen or other analgesics, resolves upon their assumption of a supine position, and returns upon sitting or standing. Photophobia and nausea can also be present. Subarachnoid hemorrhage, while also presenting as pain, is often described as the "worst headache of one's life." Furthermore, the headache of SAH is not positional and can be accompanied by changes in mental status. Because treatment of these two conditions is quite different, it is important to recognize these differentiating factors as early as possible. The often-used approach of "watching and waiting" in PDPH could lead to disastrous consequences in a case of SAH.

As a final recommendation, although most aneurysms are occult, a history indicative of an existing aneurysm, or which suggests the possibility of an existing intracranial aneurysm, should act as a restraint in administering spinal or epidural anesthesia.

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Fatal Dyspnea in a Patient with Renal Failure

Louis R. DePalo, M.D.

Abstract

A 67-year-old woman with hypertension, diabetes, hypothyroidism and chronic renal failure reported to the hospital for her regularly scheduled hemodialysis, complaining of shortness of breath. Despite fluid removal during her hemodialysis, she remained tachypneic and developed stridor. She was admitted to the hospital for a work-up of a known mediastinal mass, thought to be a goiter. However, she deteriorated over the next several hours and expired. A post-mortem examination confirmed fatal pulmonary emboli. This case illustrates the fact that, while most patients with chronic renal failure are considered to be at low risk for pulmonary emboli, it is often not diagnosed when present. In this paper, we will review the epidemiological data supporting this notion, examine proposed pathophysiological mechanisms, and review the diagnostic approach that should be considered in the setting of chronic renal failure.

Key Words: Pulmonary embolism, renal failure, CT angiogram, D-dimer.

Case Presentation

A 67-YEAR-OLD WOMAN was admitted to The Mount Sinai Hospital with shortness of breath, wheezing and hoarseness. She had a past medical history of hypothyroidism with a partial thyroidectomy 30 years previously. She also had a known mediastinal mass, presumed to be a goiter, as well as hypertension, diabetes mellitus and end-stage renal disease, for which she was receiving hemodialysis. The patient initially presented for hemodialysis; after the procedure, despite adequate fluid removal, her heart rate was 130 beats/min with both inspiratory and expiratory stridor. She was referred to the emergency department for evaluation of a possible upper airway obstruction.

She complained of severe shortness of breath, and a family member reported that she had been increasingly lethargic and anorectic during the proceeding two weeks. She was in mild respiratory distress, afebrile and normotensive, with a pulse of 110 beats/min and respiratory rate of 32 breaths/min; oxygen saturation on room air was 90% by oximetry and increased to 96% with two liters of nasal oxygen. A chest radiograph confirmed an approximately 10 x 6 cm mediastinal mass with deviation of the trachea to the right. There were no pulmonary infiltrates or effusions. The ear nose and throat (ENT) physician did not find significant upper airway compromise.

The patient was admitted to the hospital at 3 AM. Her medications included doxazosin, lisinopril, pravastatin, folate, calcium, vitamin D, ducosate and erythropoietin. Her hemoglobin was 10.5 g/dL, hematocrit 32 and platelet count 252,000/mm^3. Plasma potassium was 5.5 meq/L, and an electrocardiogram showed a sinus tachycardia with right atrial enlargement and left ventricular hypertrophy. At 3:45 AM, she complained of severe abdominal pain. She

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was noted to have pale, clammy skin. The blood pressure and pulse rate were not recorded. Her oxygen saturation fell to 86% by oximetry with 2 L of nasal oxygen. She was treated with oxygen by face mask, and nebulized albuterol. However, at 4:42AM she was found unresponsive and pulseless in her chair, and resuscitative efforts were begun. She was pronounced dead at 5:06 AM.

Autopsy demonstrated pulmonary embolism in the right lower lobe and left upper lobe, with associated pulmonary infarction. The infarct had not been recognized on an emergency room portable chest x-ray. She had atherosclerosis of the superior mesenteric artery with acute thrombosis, severe triple vessel coronary artery disease and left ventricular hypertrophy. A large posterior mediastinal goiter with no tracheal compromise was also found.

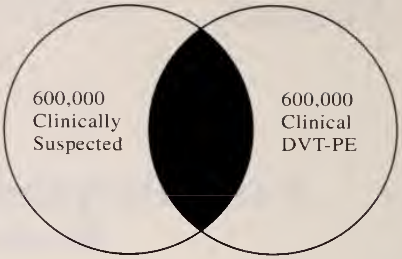

Fig. 1. Venn diagram of clinical suspicion vs. clinical occurrence. Approximately two-thirds of incidents of venous thromboembolism are asymptomatic. Two-thirds of patients presenting with typical signs and symptoms of DVT do not have the disease, which contributes to a low sensitivity and specificity of clinical diagnosis. Adapted with permission from: Wheeler HB, Anderson FA. Venous thromboembolism: Risk factors and prophylaxis. Clin Chest Med 1995; 16(2):235–251 (44).

Discussion

> *Life can only be understood backwards; but it must be lived forwards.*
>
> Kierkegaard

This patient illustrates the difficulty in making the diagnosis of deep venous thrombosis-pulmonary embolism (DVT-PE). First, in order to diagnose DVT-PE one must rank it high on the list of differential diagnoses. Second, once a diagnosis of pulmonary embolism (PE) is considered, the physician must rapidly, safely and accurately confirm and treat it in order to make a significant impact on mortality (1). Patients with renal failure have uniquely difficult diagnostic and therapeutic problems. Clinically significant PE is considered rare in patients with renal disease, and some epidemiological data support this clinical impression.

Epidemiology

The incidence of pulmonary embolism in the United States is estimated to be 600,000 cases per year, with an overall mortality of 30% (2, 3). DVT-PE is overdiagnosed for some patients and unsuspected in others (Fig. 1), leading to expensive, misdirected diagnostic evaluations for the former, and greater morbidity and mortality for the latter. The incidence of PE in patients with chronic renal failure is reported to be lower than that in the general population (4). Furthermore, the incidence of clinically significant PE in patients treated with dialysis is considered to be quite low (5). Mossey (4) reported an autopsy series of 2,255 adults from 1969–1981. Chronic renal failure was defined as a serum creatinine level greater than 5 mg/dL for six months or renal failure requiring long-term dialysis. The overall incidence of PE in this series was 32.3% (Table 1). Patients with chronic renal failure had an overall incidence of pulmonary emboli of 9.47% ($p<0.0005$) (Table 2). Significantly, all of the emboli in the renal failure group were "microscopic," with no major emboli being identified. This is in sharp contrast to the general population, where 18.4% had microscopic emboli, 4% had macroscopic emboli and 9.9% had both (Table 1). These findings must be compared to multiple autopsy series in which the incidence of PE has ranged from 6–64% (6–9). The clinical importance of these emboli, based on autopsy series, is difficult to establish; however, Dalen (1) estimated that at least 10% of those deaths were solely attributable to DVT-PE.

Pathogenesis

An accurate assessment of risk factors is an important first step in the evaluation of patients suspected of having DVT-PE. A differential distribution of these risk factors probably explains the reported difference in incidence of DVT-PE in the general population compared to patients with renal failure. Virchow's triad of "stasis" of blood flow, "intimal injury" and the "hypercoagulable" state remains the cornerstone of our understanding of the pathogenesis

TABLE 1
Incidence of Pulmonary Emboli in an Autopsy Population

Age group		Microscopic only	Macroscopic only	Microscopic and macroscopic	Total
Yr	n	n (%)	n (%)	n (%)	n (%)
18–29	42	11 (26)	0 (0)	4 (10)	15 (36)
30–39	67	11 (16)	0 (0)	4 (6)	15 (22)
40–49	181	37 (20)	4 (2)	12 (7)	53 (29)
50–59	464	78 (17)	20 (4)	41 (9)	139 (30)
60–69	568	117 (21)	19 (3)	47 (8)	183 (32)
70–79	578	103 (18)	31 (5)	64 (11)	198 (34)
>80	355	59 (17)	17 (5)	52 (15)	128 (36)
Total	2,255	416 (18)	91 (4)	224 (10)	731 (32)

n = number
Data from Mossey RT, Kasabian AA, Wilkes BM, et al., modified with permission (4).

TABLE 2
Incidence of Pulmonary Emboli in Chronic Renal Failure

Age group (years)	Patients with renal failure n	Microscopic emboli %
18–29	2	0
30–39	9	11
40–49	13	15
50–59	24	8
60–69	18	11
70–79	21	5
>80	8	18
Total	95	9

n = number of patients
No macroscopic emboli were identified.
Data from Mossey RT, Kasabian AA, Wilkes BM, et al., modified with permission (4).

TABLE 3
Risk Factors for 1,231 Patients with a Diagnosis of Acute DVT and/or PE

Risk Factor	%
Age ≥ 40 years	88.5
Obesity	37.8
History of venous thromboembolism	26.0
Cancer	22.3
Bed rest ≥ 5 days	12.0
Major surgery	11.2
Congestive heart failure	8.2
Varicose veins	5.8
Fracture (hip or leg)	3.7
Estrogen treatment	2.0
Stroke	1.8
Multiple trauma	1.1
Childbirth	1.1
Myocardial infarction	0.7
One or more risk factors	96.3
Two or more risk factors	76.0
Three or more risk factors	39.0

Data from Anderson FA, Jr, Wheeler HB, reprinted with permission (42).

of venous thromboembolism and defines the risks. Table 3 outlines known risk factors for DVT-PE, and all presuppose Virchow's three basic pathogenetic mechanisms. When there is no identifiable risk factor, it is unusual for a patient to develop venous thromboembolism. There is also convincing evidence that risk increases in direct proportion to the number of predisposing factors (10). In the retrospective review by Mossey (4), not all the known risk factors were accurately documented. The prevalence of cancer and atherosclerotic heart disease are two known risk factors for DVT-PE that were recorded but did not account for the difference observed. Other risk factors, such as prolonged bed rest, congestive heart disease and peripheral vascular disease, were not even described. However, patients with renal failure and other co-morbid conditions such as nephropathy, myopathy and diabetes would be thought to have an increased risk for PE. This suggests that uremia, unlike other chronic illness, "protects" the patient from the development of DVT-PE. The most favored explanation for the presumed decrease in DVT-PE in patients with renal failure is abnormalities of the coagulation system.

Many patients with renal failure have venous "stasis," due to their high known incidence of peripheral vascular disease, autonomic dysfunction and diabetes. *In vivo* studies suggest that "intimal injury" impairs the regulation of vascular tone by nitrous oxide (11). Chronic oxidant stress and/or low antioxidant levels (12) may also contribute to the high prevalence of vascular disease secondary to "intimal injury" in these patients. All of these impairments would predispose these patients to DVT-PE, rather than protect them from it. Certain patients with chronic renal insufficiency have acquired a "hypercoagulable" state (rheumatic conditions with antiphospholipid syndrome, nephrotic syndrome with low antithrombin III levels, etc.), but they may be exceptions to the general population of renal failure patients with lowered DVT-PE risk. Therefore, the observation of a lower incidence of DVT-PE in renal failure patients presents a paradox best explained by examining the coagulation system.

Hemostatic defects in uremia are complex and include thrombocytopenia, minor coagulation abnormalities, and platelet dysfunction. Patients with renal failure are exposed to heparin during hemodialysis, although it is unlikely that systemic anticoagulation sufficient to protect from DVT-PE is ever achieved. Graft occlusion is a common clinical event in hemodialysis patients despite heparin. Furthermore, clot dislodgement from sites of vascular access (bland or septic) is frequently reported as the recognized etiology of emboli when pulmonary embolus is suspected and diagnosed (13, 14). Platelet dysfunction is the most consistently observed abnormality in clotting and is only partially reversed with dialysis. The abnormalities of decreased platelet adherence, aggregation and secretion are best evidenced by a prolonged bleeding time. No uniform pathophysiologic mechanism has yet to emerge to explain these abnormalities. The defects in platelet function have been ascribed to accumulation of guanidinosuccinic acid (15, 16), phenol and phenolic acids (17), uremic middle molecules (18) and nitrous oxide (19). The circulating red cell mass or hematocrit modifies these defects of platelet interaction with endothelium/subendothelium. Therefore, anemia, decreased blood viscosity, and decreased platelet adherence may well be the physiologic factors protecting these patients. Finally, the two studies reporting the lowered occurrence of DVT-PE in patients with renal failure were completed before the widespread use of erythropoietin therapy. Red cell transfusion or improvement of anemia by erythropoietin therapy is associated with decreased bleeding, shortening of the bleeding time and increased platelet adhesion in hemodialyzed uremic patients (20, 21). These effects are dependent both on the increase in red cell mass and on a slight and poorly characterized effect on platelet function that is independent of hematocrit. A recent report of increased fistula thrombosis in a placebo-controlled trial of patients treated with erythropoietin (22) suggests that patients may lose the "protective" effect of anemia and platelet dysfunction and perhaps become hypercoagulable. It is reasonable to conclude that the clinical effect of erythropoietin as a risk factor for DVT-PE remains largely unknown and speculative. Furthermore, the effect of correcting anemia with erythropoietin on the reported low incidence of DVT-PE in renal failure patients deserves further study.

Diagnosis

Acute pulmonary embolism is rarely silent. With appropriate anticoagulant therapy, mortality can be decreased from 30% to less than 10% (23). However, the diagnosis of pulmonary emboli remains difficult (24). In a series of 1276 autopsies of patients who had died of PE, the diagnosis was suspected in only 31.8% of the cases while they were still alive. Paradoxically, the death rate due to DVT-PE has not declined in the last two decades despite new therapies and new diagnostic imaging techniques (25). This can be explained by the mortality of patients whose pulmonary emboli are not suspected and therefore not diagnosed. A review of the epidemiological and physiological data supports the notion of a "lower" risk for clinically significant DVT-PE in uremia. This lower risk factor, however, does not excuse the physician from continued vigilance. Indeed, with the increasing use of erythropoietin, correction of anemia and more aggressive dialytic therapies, this lower clinical risk, on historical series, will need to be re-evaluated.

Once DVT-PE is suspected, there are a number of diagnostic strategies to ascertain its presence. The PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study (26) remains the most complete prospective investigation of PE diagnosis. It accurately quantifies the diagnostic accuracy of ventilation-perfusion (V/Q) scanning, highlights the role of clinical assessment in decision making and scan interpretation, and reaffirms the safety and accuracy of pulmonary angiography. The PIOPED study also underscores the limitation of an indeterminate (i.e., nondiagnostic) scan.

However, since the publication of this landmark study and the introduction of new diagnostic tests, the diagnostic algorithm is changing. These new tests include dynamic contrast-enhanced computerized tomographic (CT) angiography, plasma D-dimer, and magnetic resonance angiography (MRA).

Extensive discussion of pulmonary embolic disease in the medical literature, combined with evidence-based decision analysis, fail to completely define clinical practice guidelines. Moser summarized the problem best (27): "Clinicians dealing with thromboembolism do not work in the literature. They work with specific patients in specific facilities with specific colleagues." Any algorithm utilizing one of the many diagnostic tests must consider these "local" factors. Many of the techniques employed depend on both operator experience (pulmonary angiography, duplex Doppler) and subjective interpretation (V/Q scanning, conventional and CT angiography). Unfortunately, technological advances (multi-slice CT scanning or MRA) are deployed and accepted before they are vigorously studied. Despite these difficulties the medical literature is replete with reasonable diagnostic strategies that can be employed with high sensitivity and specificity when used by an experienced clinician. Fig. 2 represents a typical diagnostic algorithm.

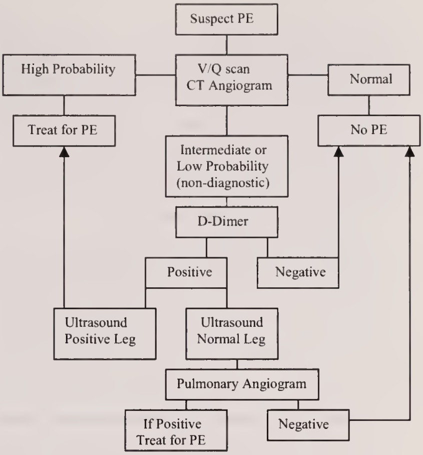

Fig. 2. *D-dimer (+) is above, D-dimer (-) is below critical threshold for exclusion of DVT-PE. Omit the D-dimer in cases of high clinical suspicion, systemic illness, or more than three days from embolism event. CT angiogram may be a substitute for ventilation/perfusion (V/Q) scan or it may follow a nondiagnostic V/Q scan. An abnormal leg ultrasound (US) or echocardiographic evidence of right ventricular hypokinesis justifies treatment without further diagnostic evaluation.

The determination of plasma D-dimer levels has been positioned as an important, early test for diagnosis of DVT-PE. Numerous reports suggest the considerable diagnostic value of plasma D-dimer levels as an indicator of active thrombosis. Van Beck et al. (28) concluded that the D-dimer ELISA assay may have a role in the exclusion of pulmonary embolism in symptomatic outpatients, where its application may reduce the need for angiography by 30% and overall medical costs by 10%. Subsequent studies using rapid (latex) D-dimer tests, which are more clinically practical, seem to confirm these results. This would position plasma D-dimer determinations as an early screening test performed upon clinical presentation of DVT-PE. D-dimer determination is widely available but remains unproven in large-scale trials, and skepticism persists (29). Wells et al. (30) argue that a simple clinical prediction model combined with D-dimer determination may safely exclude PE in a large proportion of patients for whom the diagnosis is suspected. A systematic review by Becker has been used to estimate the sensitivity and specificity of D-dimer tests (31). The reported sensitivity ranged from 48 – 96% with latex test and from 88 – 100% with ELISA test. The specificity ranged from 21 – 100% with latex test and from 10 – 68% with ELISA test. Overall, in this review, the ELISAs had greater sensitivities but lower specificities than latex. No one D-dimer test has emerged as the best. A critical review of the collective medical literature suggests that a negative D-dimer assay may be most useful, in combination with other studies, to exclude a thrombotic process.

The D-dimer determination in patients with renal disease offers a unique problem. Paradoxically, despite the known coagulation defects of uremia and chronic renal insufficiency, many studies provide evidence of plasma hypercoagulability in hemodialysis patients. This is evident, particularly in the setting of hypertension, diabetes, proteinuria and inflammatory vasculopathy. Plasma D-dimer levels are routinely elevated in patients with chronic renal failure (244 ± 31 μg/L) and diabetic nephropathy (308 ± 74 μg/L) when compared to a control population (96 ± 13 μg/L) without renal disease. Epidemiological data (4, 5) suggest that these higher levels do not imply increased risk for the development of DVT-PE. As the usefulness of plasma D-dimer is in its negative predictive value, it is unclear whether the sensitivity and specificity for this assay determined from a general population of outpatients applies to this specific subgroup. It would seem that the plasma D-dimer would be less useful in excluding DVT-PE in this population of patients, although the validity of this assay and its utility in this group are largely unknown.

The PIOPED study clearly demonstrated the diagnostic sensitivity and specificity of V/Q scanning (Table 4). V/Q scanning remains the procedure of choice for the diagnosis of pulmonary emboli. However, pretest clinical suspicion plays a major role in establishing the diagnosis of PE. Normal, high probability and low probability scans with low clinical suspicion provide accurate clinical assessments upon which sound clinical decision making can proceed. Regrettably, in the PIOPED study, only 27% of the patients had imaging studies adequate for definitive clinical decision making. The primary challenge resulting from the PIOPED data is the need to develop diagnostic strategies for the high proportion of intermediate (nondiagnostic) scans. This is particularly true given the general reluctance of physicians to perform pulmonary angiography despite evidence that it is a safe procedure with excellent diagnostic accuracy. Patients with renal insufficiency not on dialysis are an exception and require alternative diagnostic tests.

A simple strategy for patients with indeterminate, nondiagnostic V/Q scans is based on the observation (32) that patients with documented PE have a high prevalence of deep venous thrombosis (DVT) (82%). Study (Doppler, impedance plethysmography) of the deep venous system and confirmation of DVT would upgrade the finding of an indeterminate V/Q scan and obligate treatment without further need for diagnostic evaluation. Doppler ultrasound has been used to determine venous patency for more than 20 years. Barnes et al. published a series of symptomatic patients in 1975 and 1976 (33, 34), which demonstrated that Doppler examination of the lower extremity was 94% accurate when compared to venography, with a 6% false positive rate. The combination of a negative duplex Doppler study and a plasma D-dimer level below threshold value support a high negative predictive value (95%) for the absence of DVT-PE. Therefore, patients strongly suspected clinically to have PE, but with a nondiagnostic V/Q scan, a D-dimer level with high negative predictive value and a negative duplex Doppler can be followed conservatively.

Recent advances in thoracic cross-sectional imaging have led to great interest in the development of reliable, accurate techniques for diagnosing PE. There has been enthusiasm for dynamic, contrast-enhanced, spiral (helical) CT angiography, because it is quick, accessible and relatively noninvasive. Additional diagnostic information, not available from V/Q scanning, can be gained with CT techniques; it can be diagnostic of nonembolic disease. Several studies report high sensitivity and specificity for determination of pulmonary emboli with spiral CT (35–38). Spiral (helical) CT scanning is generally regarded as excellent for visualization of clots within central or segmental arteries. Critics point out major limitations, including failure to visualize subsegmental arteries (of questionable clinical significance), breathing artifact, and a high incidence of "nondiagnostic" scans. New generation scanners and multislice technologies should eliminate some of these criticisms. Table 5 shows the relative

TABLE 4

PIOPED Data — Pulmonary Embolism Status

	Clinical Science Probability (%)							
	80–100%		20–79%		0–19%		All Probabilities	
Scan Category	n with PE / N	%	n with PE / N	%	n with PE / N	%	n with PE / N	%
High probability	28/29	96	70/80	88	5/9	56	103/118	87
Intermediate probability	27/41	66	66/236	23	11/68	16	104/345	30
Low probability	6/15	40	30/191	16	4/90	4	40/296	14
Near normal/normal	0/5	0	4/62	6	1/61	2	51/128	4
Total	61/90	68	170/569	30	21/228	9	252/887	28

n = number of patients, N = number in group

PE indicates angiogram reading that shows pulmonary embolism or positive determination by committee review.

Data from PIOPED Investigators, modified with permission (26).

TABLE 5
Spiral CT versus Angiography

Investigators	n	Sensitivity (%)	Specificity (%)
Remy-Jardin et al. (1992) (35)	42	100	96
Goodman et al. (1995) (37)	20	86*	92*
	63	89	
Remy-Jardin et al. (1996) (38)	75	91*	78
Drucker et al. (1998) (36)	47	60	81
Interpreted by 2 groups		53	97

n = number of patients
* For central pulmonary emboli. Other percentages are for all pulmonary emboli
Data from Holbert JM, Costello P, Federle MP, modified with permission (43).

sensitivity of spiral CT compared to conventional pulmonary angiography in 4 studies. Sensitivity ranges from 53–100% and specificity ranges from 78–97%. When only central and segmental artery clots are evaluated, sensitivity and specificity are approximately 90% in most studies. However, no large-scale outcomes study similar to PIOPED exists. Most of the patients examined are in a highly selected population with motivated radiologists; results with less highly selected patient population may not be comparable. Woodard (39), in her editorial following publication of early CT trials, suggests that the high sensitivity and specificity may be misleading, and urges caution. Although nominally less invasive than angiography, the radiocontrast dose is significant and, therefore, equally problematic in patients with renal failure not on dialysis. Finally, a nondiagnostic CT angiogram may require further dye exposure (pulmonary angiogram) and cause delay in diagnosis.

Concerns about contrast-induced worsening of renal failure and the need for postcontrast dialysis for patients on chronic hemodialysis are a major impediment to the diagnosis of DVT-PE in patients with chronic renal insufficiency. Magnetic resonance imaging (MRI) and MRA have been employed, but initial results were poor because of respiratory-motion artifact and poor contrast between flowing blood and emboli. The use of faster magnetic resonance hardware combined with dynamic gadolinium enhancement now allows for high resolution imaging in a single breath-hold. Preliminary results are promising (40, 41); however, more studies are needed to identify accurately the sensitivity and specificity of this technique in comparison to other imaging technologies. MRA may be a reasonable first step in diagnosing pulmonary embolus in renal-failure patients in whom contrast may be contraindicated.

Summary

"Be careful to get out of an experience all the wisdom that is in it; Not like that cat that sits down on a hot stove. She will never sit down on a hot stove lid again ...and that is well; But also she will never sit down on a cold one anymore."
Mark Twain, *Huckleberry Finn*

The case reviewed here demonstrates that suspicion for PE must be maintained despite the notion and assertion that chronic renal failure patients are at low risk for DVT-PE. This is surprising, considering the chronic nature and co-morbid diseases associated with chronic renal failure. Furthermore, certain markers of plasma hypercoagulability would suggest increased rather than diminished risk. Defects in hemostasis, specifically in platelet function, may explain this paradox. This risk may also be increased with the introduction of erythropoietin to raise hematocrit levels. Diagnosis remains difficult, particularly in patients with renal diseases. Newer and less invasive techniques offer some promise for achieving a definitive diagnosis but must be used with an appreciation of their limitations.

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Management of Stroke and Transient Ischemic Attack

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Abstract

Stroke is a major cause of death and disability. The resulting burden on society continues to grow, despite recent advances in acute stroke therapy. Thrombolysis reduces stroke morbidity but is only applicable to a small percentage of stroke patients. Acute stroke units, which allow for the greatest overall improvement in outcome, provide the best facilities for acute intervention. Despite recent advances in acute management, such as endarterectomy and anticoagulation, primary and secondary preventive measures to control stroke risk factors, along with appropriate specific interventions, are the key to reducing the overall burden of stroke.

Key Words: Stroke, treatment, prevention, transient ischemic attack.

Stroke is a major public health problem, primarily afflicting older adults. It is the third leading cause of death in the United States. Worldwide, the mortality rate from stroke is surpassed only by that of heart disease (1, 2). In the U.S., more than 700,000 new strokes occur annually (3). Stroke is also the leading cause of disability in the U.S., with an estimated 4 million stroke survivors in this country living with stroke-related deficits (1). More than 70% of stroke survivors remain vocationally impaired, more than 30% require help with activities of daily living, and more than 20% walk only with assistance (4). Approximately half of all stroke survivors return to some form of employment, but this figure declines with age (5). Moreover, the incidence of stroke doubles in each successive decade after age 55. Until age 75 it is more common in men than in women, but after 75 it is equally common in both groups. Half of all strokes occur in people older than 75 years, and age is the most important risk factor for stroke (3, 6, 7). Therefore, as the population in this country ages, the burden of dealing with stroke will grow, in terms of caring for an ever-increasing number of new stroke patients and stroke survivors. The discussion that follows focuses on four strategies for reducing that burden.

Ischemic Stroke Subtypes

There are three main subcategories of cerebral infarction: (a) cardioembolic, (b) large vessel atherothrombotic, and (c) small vessel or lacunar stroke. Although the treatment of the acute form of each subtype may not differ markedly, there is some suggestion that the efficacy of therapy may differ by subtype. More significantly, preventive measures are determined by the presence of risk factors or co-morbid conditions that are associated with the particular stroke subtype.

Cardioembolic Infarction

Embolism from thrombi that form in the heart and those that occur in large veins and

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pass through the heart via a right-to-left shunt account for approximately 30% of ischemic strokes. A variety of cardiac sources of embolism have been identified, including valvular lesions, hemostasis secondary to rhythm disturbances, and hypokinesis of the left ventricle, either globally as in a cardiomyopathy or focally, secondary to infarction. Atrial fibrillation is the most widely recognized cardiac abnormality associated with ischemic stroke. It is a condition of the elderly, occurring in 0.1% of those 50–59 years of age, but increasing gradually to 4% of those over age 80. The proportion of strokes attributed to atrial fibrillation also increases with age, rising from 7% of strokes for patients in their sixth decade, to 36% for those in their ninth decade (8). The development of transesophageal echocardiography (TEE) has made it possible to detect thrombi in the left atrial appendage, the site that generally harbors a clot in a fibrillating atrium. These thrombi are not visible on transthoracic echocardiogram. A patent foramen ovale (PFO), the most common conduit for paradoxical emboli, is also readily diagnosed by TEE, as is atherosclerotic plaque in the ascending aorta and aortic arch of elderly patients. These plaques can be ulcerated and serve as a nidus for clot formation, or protrude into the lumen as a highly mobile peduncle, likely to embolize to more distal arteries. The thickness of this plaque has been correlated with the risk of stroke (8–10).

Lacunar Infarction

Lacunae are small, deep infarcts caused by degenerative changes within small penetrating arteries that bring blood to the internal capsule, basal ganglia, cerebral white matter, thalamus, and pons. In various series and registries, they account for at least 25% of ischemic strokes and are the most common vascular lesions found within the brain at autopsy. Hypertension is the most important risk factor for lacunar infarcts. The neurologic symptoms depend on the region of ischemia. The most common clinical presentations are: (a) pure motor stroke due to ischemia in the pons or internal capsule which is characterized by weakness of the face, arm, and leg on one side of the body; (b) pure sensory stroke due to infarction in the lateral part of the thalamus and/or posterior limb of the internal capsule which is characterized by numbness or paresthesia of the face, arm, leg, and trunk on one side of the body, without weakness; (c) ataxic hemiparesis due to infarction in the subcortical white matter or pons which is characterized by a combination of incoordination and weakness on one side of the body; and (d) clumsy hand-dysarthria due to pontine infarction which is characterized by markedly slurred speech and difficulty with fine motor control of one hand (11). The diagnosis of lacunar infarction is based on the presence of risk factors, the nature of the clinical signs and symptoms, and the results of neuroimaging tests.

Large Artery Occlusive Disease

The large vessels that bring blood into the brain are prone to atherosclerotic narrowing, most commonly at sites of origin or bifurcation, especially the bifurcation of the common carotid into the internal and external carotid arteries in the neck. Atherosclerotic stenosis leads to infarction by reducing blood flow distal to the point of stenosis and by acting as a nidus for adhesion and aggregation of platelets, producing either thrombosis at that location or embolization to and occlusion of more distal, narrower arteries. The neurologic symptoms will depend upon the artery affected. In general terms, these symptoms can be divided into those that arise from the anterior (carotid) circulation, supplying the anterior three-fourths of each hemisphere, and those that arise from the posterior (vertebrobasilar) circulation, supplying the occipital lobes, posterior thalamus, cerebellum and brainstem.

Symptoms and signs referable to the anterior circulation include contralateral weakness, numbness and visual deficits. If the left hemisphere is affected, aphasia is common, while right hemisphere lesions produce behavioral disturbances. Symptoms and signs of posterior circulation ischemia are highly variable and overlap with those of the anterior circulation. Vertigo, diplopia, nausea and vomiting are common complaints in brainstem or cerebellar disease. Nystagmus, disconjugate eye movement abnormalities, gait or limb ataxia, crossed (i.e., ipsilateral face and contralateral limb or body) sensory or motor deficits and hemianopic visual field loss are indicative of posterior circulation ischemia.

Treatment of Acute Infarction

The purpose of acute stroke treatment is to reduce death and disability from that event. Until recently there was no proven effective therapy. In June 1996, the Food and Drug Administration (FDA) approved the intravenous administration of tissue plasminogen activator (t-PA) in acute ischemic stroke, given within three hours of symptom onset. This signaled a virtual revolution in the diagnosis and management of acute stroke. For the first time a proven, safe and effective treatment is available, but the time frame for its effective use requires a much more expeditious response than was customary for patients, emergency medical services, doctors and hospitals. Thus, it is now necessary for the public to be educated in order to recognize a stroke and react appropriately, particularly since only one-third of patients experiencing a stroke recognize it as such. Health care providers must also be educated to respond to stroke as an emergency. Once the patient is at the hospital, prompt triage is necessary. It is crucial to determine the time of symptom onset and the presence of signs of trauma or medical conditions that would predispose to a particular stroke type, or that would preclude the use of t-PA. A computed tomography (CT) scan must be performed as quickly as possible, to exclude intracranial hemorrhage or a non-ischemic cause of the patient's symptoms, such as a brain tumor or subdural hematoma.

The evidence that intravenous administration of t-PA is an effective treatment for acute ischemic stroke comes from the National Institute of Neurological Disorders and Stroke (NINDS)-NIH t-PA Stroke Study, in which 624 patients were treated with 0.9 mg/kg of t-PA within 3 hours of onset; half were treated within 90 minutes. Patients treated with t-PA were 30% more likely to have minimal or no disability three months later. The major risk of treatment was intracerebral hemorrhage, which occurred in 6.4% of patients treated with t-PA but in only 0.6% of those who received placebo. Mortality was similar in both groups (17% t-PA, 20% placebo). Patients with the three major stroke subtypes benefited similarly (12). Unfortunately, only 2–5% of ischemic stroke patients are currently treated with intravenous t-PA, since most arrive at a hospital later than three hours after onset.

In two other large, randomized trials with longer treatment windows, t-PA was not more effective than placebo, although post-hoc analyses suggest there may be a benefit beyond three hours if patients are appropriately selected (Table).

TABLE

Characteristics of Patients with Stroke Who May Be Eligible for Intravenous Tissue Plasminogen Activator Therapy

Age ≥ 18 yr
Diagnosis of ischemic stroke causing clinically apparent neurologic deficit
Onset of symptoms less than 3 hours earlier
No stroke or head trauma during the preceding 3 months
No major surgery during the preceding 144 days
No history of intracranial hemorrhage
Systolic blood pressure ≤ 185 mm Hg
Diastolic blood pressure ≤ 110 mm Hg
No rapidly resolving symptoms or only minor symptoms of stroke
No symptoms suggestive or subarachnoid hemorrhage
No gastrointestinal or urinary tract hemorrhage within the preceding 21 days
No arterial puncture at a noncompressible site within the preceding 7 days
No seizure at the onset of stroke
Prothrombin time ≤ 15 sec or international normalized ratio ≤ 1.7, without the use of an anticoagulant drug
Partial-thromboplastin time within the normal range, if heparin was given during the preceding 48 hours
Platelet count ≥ 100,000/mm^3
Blood glucose concentration > 50 mg/dL (2.7 mmol/liter)

(Adapted from: TPA Stroke Study Group Protocol Guidelines)

Intra-arterial thrombolysis, in which a microcatheter is advanced to and sometimes through the obstructing clot has gained increased acceptance because of a recent randomized trial. This procedure is available only at selected centers. A $2^{1}/_{2}$-year multicenter trial (PROACT II) demonstrated that patients with arteriographically confirmed occlusion of the middle cerebral artery (MCA) or its two main branches, who received intra-arterial thrombolysis with prourokinase within six hours of onset, had better outcomes three months after the stroke than did those who received only low-dose intravenous heparin (13). Because prourokinase is not commercially available, most centers that perform intra-arterial thrombolysis use t-PA. No randomized trials of intra-arterial thrombolytic therapy for vertebrobasilar disease have been completed, but several reports of improved outcome relative to the usual poor prognosis in this condition have led many authorities to recommend its use, particularly in patients who cannot be treated with intravenous t-PA within three hours of onset.

Antithrombotic Therapy

Over the past thirty years, anticoagulation with continuous intravenous infusion of unfractionated heparin has probably been the most widely used treatment for acute stroke, yet to date, no clinical trial has adequately tested its efficacy. Recently several trials of anticoagulation by varying methods have reported conflicting results. The International Stroke Trial (IST) enrolled nearly 20,000 patients within 48 hours of symptom onset in a 3 x 2 factorial design. These patients received subcutaneous heparin at a dose of 5,000 or 12,500 IU twice daily, or no heparin, with or without 300 mg of aspirin daily (14). There were no differences in the primary outcome measures (death at 14 days; death or dependency at 6 months) among any of the treatment groups. There was, however, an increased risk of hemorrhage in the high-dose heparin group. This study has been criticized because of the unconventional (by American standards) method of heparin administration, lack of monitoring of anticoagulant effect, lack of blinding and failure to obtain neuroimaging before randomization and initiation of treatment.

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) evaluated the low-molecular-weight heparinoid, danaproid, versus placebo; 1,281 ischemic stroke patients were treated with continuous intravenous infusion for seven days, beginning within 24 hours of symptom onset. There was no significant reduction in stroke progression, 7-day mortality, or risk of stroke recurrence. In a subgroup analysis, there appeared to be a better 3-month outcome in the large vessel atherosclerotic subgroup (68% vs. 55% favorable outcome) (15). Another double-blind, placebo-controlled trial randomized 2,750 patients to a high or low dose of a different low-molecular-weight heparin (LMWH), nadroparin, or placebo subcutaneously, begun within 48 hours of symptom onset (16). There was a significant dose-dependent effect among the three study groups in favor of the LMWH. The main outcome measure was death or dependency, defined as requiring the help of others to perform activities of daily living after six months (16).

The Heparin in Acute Embolic Stroke Trial (HAEST) compared the LMWH dalteparin 100 IU/hg twice daily to aspirin 160 mg once daily, begun within 30 hours of symptom onset, for 449 patients with acute ischemic stroke and atrial fibrillation. There was no difference in the frequency of stroke recurrence in the first 2 weeks following stroke, and no difference in functional outcome at 2 weeks or 3 months (17).

Despite the lack of evidence supporting its use, intravenous unfractionated heparin remains in widespread use for patients not eligible for thrombolysis, especially those with presumed cardioembolic infarction, antiphospholipid-antibody syndrome, extracranial carotid or vertebral artery dissection, cerebral vein thrombosis and impending large vessel thrombosis. It is usually given as a continuous intravenous infusion with a goal of maintaining the partial thromboplastin time at 1.5 – 2.0 times normal.

Antiplatelet Therapy

Early treatment with aspirin is commonplace for patients not treated with thrombolysis or anticoagulation. This practice arose because aspirin was of proven benefit in secondary stroke prevention and in the acute management of myocardial ischemia. Recently, two trials evaluated its benefit in a total of more than 40,000 patients treated within 48 hours of stroke onset. In the IST, although there was no difference in the primary outcome measures among treatment groups, secondary analyses demonstrated a small decrease (2.8% vs. 3.9%) in the rate of recurrent ischemic stroke in patients treated with aspirin. The Chinese Acute Stroke Trial randomized 21,106 patients to aspirin 160 mg once daily, or placebo, for four weeks. A slightly lower mortality rate (3.3% vs. 3.9%) and recurrent stroke rate (1.6% vs. 2.1%) were demonstrated in the aspirin group (18).

Other oral antiplatelet drugs (e.g., clopidogrel, dipyridamole, ticlopidine), effective in secondary prevention, have not been studied in acute stroke. A phase II study of abciximab, a GPIIb/IIIa-receptor antagonist effective in acute myocardial infarction (MI) and in coronary artery stenting procedures, demonstrated safety and showed a trend toward better outcomes in the treated group. A phase III study is underway (19).

Neuroprotection

Ischemic neuronal death results from a cascade of events set in motion by an inadequate supply of oxygen and nutrients. As the understanding of the process grows, so does interest in drugs that may interfere with one or more steps in the process. However, several approaches that showed promise in laboratory models have foundered in clinical trials. Potential neuroprotective agents, such as dihydropyridine-calcium channel blockers (nimodipine), N-methyl-D-aspartate-receptor antagonists (aptiganel), antibodies to intercellular adhesion molecules (elinomab), free radical scavengers (lubeluzole) and other agents with multiple putative mechanisms of action (citicholine, clomethiazole), have failed to show efficacy in phase III trials. Various explanations, including adverse effects limiting tolerable doses, inadequate delivery of drug to ischemic tissue and delay in administration, have been given for the failure to replicate in clinical stroke the favorable responses found in laboratory models. Although research continues and enthusiasm is high for the discovery of a potentially effective agent or combination of agents, no effective neuroprotective agent has yet been demonstrated (20).

Acute Stroke Units

Thrombolysis is currently the most dramatic and effective form of acute stroke therapy, but is applied to only about 2% of all strokes in the United States. Aspirin therapy is more widely applicable, and while statistically it was significantly better than placebo in two large trials, its use resulted in an absolute risk reduction of only about 1% in the outcome events measured. Since aspirin can be administered to most patients, its use would result in preventing three times as many deaths or dependent outcomes than can be avoided with thrombolytic therapy. However, this still translates into treating 100 patients in order to prevent one poor outcome. Anticoagulation is still widely used, but is of no proven benefit. By far the most widely applicable and effective acute stroke intervention is the use of dedicated acute stroke units. In randomized trials, this approach was shown to reduce death or dependency from stroke to the same degree as does thrombolysis, and it is applicable to all stroke patients (21).

The facilities offered by acute stroke units vary from site to site and from country to country. Some focus on the initial 48 hours, while others include rehabilitation programs. Numerous studies have demonstrated their effectiveness in providing general medical or neurologic services. While the characteristics of these units may vary, they all share an integrated approach to patient care, in which physician, nurse and therapist (e.g., speech, physical, or occupational) are involved primarily in the care of stroke patients, work together as a team, and provide close monitoring and rapid assessment and treatment of the patient. As a result, short-term and long-term mortality rates are lower and hospitalizations are shorter. And the overall cost of the illness is reduced (22).

Secondary Prevention

Individuals who have experienced a stroke or transient ischemic attack (TIA) are at markedly increased risk of stroke. In the first year after a TIA or stroke, the risk of stroke is approximately 10%. The cumulative three-year risk is approximately 25%. Preventive therapy should be targeted at the appropriate pathophysiologic mechanism which corresponds to the stroke subtype. There are three specific therapies of proven benefit in preventing a secondary stroke: carotid endarterectomy; anticoagulation of patients with atrial fibrillation; and platelet anti-aggregant therapy, if anticoagulation is not employed. Antiplatelet therapy has not been shown to be effective in primary prevention, but the other two treatments are effective in primary prevention in selected populations, as discussed below.

Cardioembolic stroke occurs most commonly in the setting of atrial fibrillation. Multiple trials comparing anticoagulation with warfarin to placebo, or to treatment with aspirin, have demonstrated the clear superiority of warfarin; however, these trials have excluded patients with prior stroke. The European Atrial Fibrillation Trial, however, randomized 669 patients with recent TIA or minor stroke to receive either warfarin or 300 mg of aspirin, and demonstrated an annual stroke risk reduction of from 12% for those treated with aspirin to 4% in the anticoagulated patients (23). Similarly, in the subgroup of patients with previous thromboembolism in Stroke Prevention in Atrial Fibrillation III (SPAF III), the rates of primary events (ischemic stroke or systemic embolism) were 11.9% per year with combination therapy (aspirin 325 mg plus fixed-dose warfarin set after achieving an international normalized ratio [INR] of 1.2 – 1.5 on two successive measurements) and 3.4% per year with adjusted-dose warfarin (target range INR = 2.0 – 3.0) (24).

Cardioembolic strokes can also occur in association with acute myocardial infarction, particularly when they involving the anterior wall, mitral valve prolapse, patent foramen ovale, and prosthetic mechanical heart valves. Patients with atrial fibrillation and mitral stenosis, and patients with mechanical heart valves are generally treated with warfarin with a target INR range of 3.0 – 3.5 (25). Anticoagulation may be used to prevent stroke recurrence in the setting of presumed paradoxical embolus from PFO, for stroke thought to be secondary to an underlying hypercoagulable state, or for stroke secondary to intracranial arterial stenosis, although there is no clear evidence yet available regarding optimum treatment for these conditions.

Carotid Stenosis

Narrowing of the lumen of the internal carotid artery is associated with an increased risk of stroke. A residual lumen that is less than 20% of normal diameter correlates highly with the development of total occlusion of the internal artery or the development of symptoms related to that artery (26). Endarterectomy is the specific treatment most widely used for this condition. In the past decade, several large-scale randomized trials involving symptomatic and asymptomatic individuals have provided data that allow a rational selection of appropriate patients for this procedure. In both the European Carotid Stenosis Trial (ECST) (27) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (28), individuals with symptoms referable to a highly stenotic carotid artery clearly benefited from surgery. The ipsilateral stroke rate in the nonsurgical arm was 22% in ECST and 26% in NASCET, but in the surgical arm in these patients it was only 10% and 9% respectively. Individuals with moderate symptomatic stenosis had stroke rates approximately one-half those of the highly stenotic groups. While the benefit of surgery in reducing subsequent stroke risk in the symptomatic highly stenotic groups was clearcut, this benefit disappeared once the degree of stenosis was less than 50% by NASCET criteria (comparable to approximately 75% by ECST criteria) (29). In the Asymptomatic Carotid Atherosclerosis Study, the overall benefit of carotid endarterectomy to asymptomatic individuals with at least 60% stenosis was statistically significant but less dramatic. Women with asymptomatic carotid stenosis may not benefit from endarterectomy at all (30).

Antiplatelet Therapy

A majority of cerebral ischemic events, whether transient or persistent, are due to thrombosis or thromboembolism. Several trials have demonstrated the efficacy of a variety of antiplatelet and antithrombotic agents in the secondary prevention of stroke among persons at high risk as a result of previous TIA or ischemic stroke. These agents have been shown to reduce the risk of subsequent stroke. After a TIA or stroke, the risk of stroke is high, particularly in the first 30 days, and it remains elevated over time. There is a 40% rate of subsequent stroke within 5 years (31).

The Antiplatelet Trialists' Collaboration was a meta-analysis of 17 trials intended to determine the efficacy of antiplatelet treatment (with any agent) in various populations at risk for vascular events. This analysis showed that antiplatelet agents reduced the odds of nonfatal stroke, MI or vascular death by 22% for persons with a history of TIA or stroke. The benefit was seen in men and women of all ages, with or without hypertension or diabetes mellitus. Long-term antiplatelet therapy was seen to prevent about 36 serious vascular events per 100 patients treated for 3 years (32).

In the past decade, several other antiplatelet agents have been widely used for secondary prevention of stroke (33). Clopidogrel was studied in the "Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events" (CAPRIE) trial, a single trial including patients with atherosclerotic vascular disease, defined as prior MI, stroke or peripheral vascular disease. The annual incidence of stroke, MI or vascular death was 5.83% in the aspirin group and 5.32% in the clopidogrel group, an 8.7% (p=0.05) relative risk reduction. Among patients with prior stroke, there was a nonsignificant reduction in the incidence of these vascular outcomes (7.71% with aspirin vs. 7.15% with clopidogrel). In two large randomized trials, compared with placebo, ticlopidine significantly reduced the risk of stroke, MI or vascular death. In the Ticlopidine Aspirin Stroke Study (TASS), compared with high-dose aspirin in patients with TIA or minor stroke, ticlopidine provided a 12% reduction (p=0.05) in the risk of stroke or death, and a 21% reduction (p=0.02) in the risk of fatal or nonfatal stroke at 3 years for patients with TIA or minor stroke (34). For fatal or nonfatal stroke, the cumulative event rate at one year was 4.8% for patients receiving ticlopidine and 7.5% for those receiving aspirin. Minor stroke was the qualifying event in 927 patients (463 on ticlopidine, 464 on aspirin) entered in TASS. Among these patients, the cumulative event rate at one year for nonfatal stroke or death was 6.3% for those receiving ticlopidine and 10.8% for those receiving aspirin (42% risk reduction). The Canadian American Ticlopidine Study (CATS) randomized patients with mild or moderate, non-cardioembolic stroke to ticlopidine or placebo. Ticlopidine was more efficacious than placebo in preventing recurrence (11.4% stroke or stroke death per year in the placebo group vs. 7.8% in the ticlopidine group) (35). In the European Stroke Prevention Study-2 (ESPS-2) (36), the combination of low-dose (25 mg) aspirin and extended-release dipyridamole (200 mg) (Aggrenox) twice daily was twice as effective for stroke prevention as was either drug alone. There was a 15% risk reduction relative to placebo with either drug alone and a 30% reduction with the combination. The 24-month stroke-free survival rate was 84.2% in the placebo group, 86.8% in the dipyridamole group, 87.1% in the aspirin group and 90% in the combination-therapy group. A comprehensive review by the Cochrane Collaboration of all published studies indicated that thienopyridine derivatives (ticlopidine, clopidogrel) are modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk (specifically for TIA/ischemic stroke), but suggested there is uncertainty about the size of this additional benefit (between 3 and 28 strokes avoided per 1,000 patients treated for 2 years) (37).

There is no single definitive trial establishing the optimal aspirin dose for preventing stroke and other vascular events in persons with prior TIA/stroke. A meta-analysis of aspirin trials for patients with cerebrovascular disease revealed a 15% overall relative risk reduction for stroke, which appeared uniform across dosages ranging from 50 – 1500 mg daily (38).

In response to the evidence indicating the efficacy of low-dose aspirin for stroke prevention, the FDA issued new professional labeling for aspirin that indicates that the appropriate dose for stroke prevention after TIA or stroke is 50 – 325 mg daily. The American College of Chest Physicians has issued similar guidelines for first-line preventive treatment after noncardioembolic TIA or stroke, suggesting that there are no important differences in daily doses of aspirin between 30 mg and 1300 mg in the prevention of stroke and other vascular events (39).

Antiplatelet therapy is the most commonly prescribed stroke prevention remedy and is usually appropriate for any symptomatic individual who does not require anticoagulation. Most patients are maintained on enteric-coated aspirin, and 325 mg daily is the most commonly prescribed dose in the United States. However, as the above data suggest, there is no consensus regarding the optimal dose, with the most recent recommendations suggesting a range of 50 – 325 mg (40). However, other authorities suggest that higher doses, if tolerated, are more effective (41). The newer medications may have somewhat greater efficacy than aspirin, but the cost for an individual in the U.S. is currently in excess of $1,000/year when the drug is purchased at a retail pharmacy. Since the differences among various agents are small when compared with the effect of taking no antiplatelet agent at all and compliance has been shown to be a major problem, encouraging patients to be compliant and maintaining compliance with the prescribed regimen, is likely to be the most effective therapeutic intervention.

Primary Prevention

Although effective treatment of acute stroke is available, prevention is far better. Effective prevention consists of addressing stroke risk factors and treating specific etiopathologic mechanisms identified in a given individual. Patients with prior TIA or stroke are at markedly increased risk of stroke and benefit most from specific interventions. However, primary prevention (treatment of individuals free of cerebrovascular disease) by treatment of stroke risk factors is also effective in reducing an individual's stroke risk.

Hypertension

Hypertension is the most important modifiable stroke risk factor. This was first demonstrated by investigators in The Framingham Heart Study, who found that stroke risk increased in proportion to both systolic and diastolic blood pressures throughout the measured range (42). This effect has been found to be consistent in many populations (43). Subsequent studies have demonstrated that reduction of blood pressure lowers stroke risk (44). Treatment of isolated systolic hypertension is also clearly beneficial, especially in the elderly (45, 46). The choice of specific antihypertensive agent is less important than actually obtaining satisfactory control and should be determined by individual patient characteristics. However, a recent study suggested that an angiotensin-converting-enzyme (ACE) inhibitor may provide stroke protection beyond its antihypertensive effect (47). Since ACE inhibitors are generally well-tolerated in the elderly, this class of agents should be considered as the initial antihypertensive treatment in a stroke-prone individual. Recently published national guidelines suggest blood pressure of less than 140/85 mm Hg (135/80 in diabetics) as the appropriate treatment goal (48). The effect of angiotensin receptor blockers has not been studied.

Hyperlipidemia

Elevated serum cholesterol is an important risk factor for coronary artery disease, but its role in stroke is unclear. The Multiple Risk Factor Intervention Trial (MRFIT) screened 351,000 men and demonstrated a curvilinear relationship, in which serum cholesterol of more than 240 mg/dL was associated with an increased risk of ischemic stroke mortality, while a level of less than 140 mg/dL was associated with an increased rate of intracerebral hemorrhage (49). However, in a meta-analysis of 45 studies, the Prospective Studies Collaboration failed to find a relationship between total cholesterol and stroke among 450,000 individuals (50). Similarly, neither the Framingham Study (51) nor the Cardiovascular Health Study (52) demonstrated a relationship between cholesterol and stroke. Consistent with these primarily negative findings, early cholesterol reduction studies showed a beneficial effect on heart disease, but not on stroke. Surprisingly, results in more recent trials using hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors consistently demonstrated a relative risk reduction of 20–30% for stroke in patients with coronary artery disease, which is similar to the risk reduction demonstrated for the various cardiovascular events studied (53, 54). This seemingly paradoxical finding may be explained by the putative beneficial effects of statins on platelets, plaque stabilization, smooth muscle cells, endothelial cell function, and inflammation, in addition to lowering low-density lipoprotein (LDL) cholesterol (55). The effect of triglycerides on stroke risk is also unclear, but a recent study of gemfibrozil demonstrated a similar degree of stroke risk reduction with minimal effect on high-density or low-density lipoproteins, but significant lowering of triglycerides. This suggests that triglycerides may also play a more significant role in stroke than previously recognized (56).

Other Factors

The Framingham Study was also among the first prospective cohort studies to demonstrate an increased stroke risk for cigarette smokers. Smokers had twice the risk of stroke as nonsmokers, but that risk was eliminated within about two years of cessation of smoking (57).

Most studies have shown an increased risk of stroke with heavy alcohol consumption, but recently, moderate consumption (< 2 drinks/day) has been shown to be protective against stroke (58). While urging heavy drinkers to decrease or eliminate their alcohol consumption is advisable for many reasons, the idea of encouraging nondrinkers to begin is controversial.

Elevated levels of homocysteine in the blood (hyperhomocysteinemia) has recently been associated with increased risk of stroke and myocardial infarction (59). Individuals with levels above 15 μmol/L appear to have five times the risk of stroke as compared to those with levels below 10 μmol/L. The efficacy of reducing stroke risk by lowering blood homocysteine levels with a combination of vitamins B_6, B_{12} and folic acid is currently being assessed (60), but at least recommending the use of a multivitamin containing these elements, especially by the elderly, appears prudent.

A substantial increase in the age of our population will, unfortunately, lead to an increased incidence of stroke, especially recurrent stroke. Advances in acute stroke treatment will reduce the degree of damage caused by strokes and also reduce case fatality rates, but prevention, both primary and secondary, will remain the most effective means of reducing the overall burden of stroke on our society.

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Editor's Note

In response to comments and suggestions raised by referees, the authors were asked to comment on the diagnostic role of electron-beam computer tomography (EBCT) in clinical practice and its clinical utility for screening patients with chest pain who are at risk for coronary artery disease. The American College of Cardiology and the American Heart Association sponsored the publication of a consensus document which reviewed the then-current literature (1) on the use of EBCT for the diagnosis and prognosis of coronary artery disease. In a recent article, Lee and Boucher (2) did not mention EBCT. Drs. Eltzschig and Ehlers, in a letter to the editor (3), called attention to studies which concluded that EBCT was useful in detecting coronary artery disease, with high sensitivity and specificity, and that the technique offered substantial cost savings. Lee, however, in his reply (4), stated that the clinical role for EBCT and its effect on patients' outcome have not yet been determined.

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Imaging of Coronary Artery Calcification

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Abstract

Coronary artery disease is a leading cause of morbidity and mortality among Americans. The traditional methods of evaluating coronary artery disease rely on the evaluation of the patient's symptoms and the presence of advanced disease. Until recently there was no method of early screening for coronary atherosclerosis in an asymptomatic population. However, calcification is a recognized marker for disease and is sometimes a component of the atheromatous plaque. With the advent of electron-beam computed tomography and subsecond helical computed tomography, a method of screening for and quantitating the amount of coronary calcification has been developed. The coronary calcium score is based on both the area and density of the calcification. This methodology can identify patients at risk for coronary artery disease, so that risk factor modification and preventive therapy can be initiated early in the course of the disease.

Key Words: Coronary artery disease, atherosclerosis, electron-beam computed tomography, computed tomography, coronary artery calcification.

Introduction

Coronary heart disease (CHD) is the leading cause of death among Americans. American Heart Association statistics (1) document more than 459,000 deaths from CHD in 1998. Of these deaths, 220,000 occurred before the victims could be hospitalized; they were often sudden deaths. It is estimated that this year 1,100,000 Americans will have a coronary event (myocardial infarction or fatal CHD). A 1995 study calculated that primary prevention of myocardial infarction could prevent more than 100,000 deaths in the United States each year (2). Therefore, the detection of coronary heart disease early in its course is of great potential importance. Yet, established risk factors fail to predict approximately one-third of future deaths due to coronary heart disease (3). Moreover, the current noninvasive methods of detecting CHD due to coronary artery disease (CAD), such as exercise treadmill testing and myocardial single-photon-emission computed tomography (CT), depend on the presence of advanced stenoses within the coronary arteries.

Calcification is closely associated with atheromatous plaque, and is a recognized marker for coronary artery disease (4–7). In recent years, a new generation of CT scanners was developed that can acquire images very rapidly. These scanners, called electron beam scanners, can eliminate motion artifact from the heart and clearly image the coronary arterial tree and possible coronary calcification. This type of scanner is highly sensitive, making it an excellent tool for detecting coronary atherosclerosis, so that preventive strategies and risk modification can be implemented to decrease morbidity and mortality.

Pathophysiology of Coronary Artery Atherosclerosis and Calcification

The etiologic mechanism of coronary artery atherosclerosis has been studied in detail in re-

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cent years. As a result, our knowledge of the process has grown considerably. The most widely held theory is based on the "response to injury" hypothesis (8). The essential element of this hypothesis states that injury to the endothelial cells, which induces a chronic inflammatory response, leads to atherosclerosis. This response of the endothelial cells leads to the various types of atherosclerotic lesions (9, 10).

The earliest lesions begin in childhood and are known as fatty streaks. They consist predominantly of macrophages that have migrated into the intima of the vessel. However, a variable amount of smooth muscle cells can also be found in the lesions. Both cell types in these lesions are rich in lipid content; calcium can be detected within the lipid core. Fatty streaks are sessile and cause no obstruction to the artery. They have no clinical sequelae. In fact, these lesions are found in all young adults, including those who do not develop occlusive atherosclerotic disease.

The formation of fibrous plaque is the next step in the progression of atherosclerosis. It is characterized by the migration and proliferation of smooth muscle cells into the intima. These cells form a fibrous cap over the deeper layer of lipid-laden macrophages by depositing connective tissue matrix as well as intracellular and extracellular lipids. Again, calcium can be found in these lesions. The fibrous plaque is an elevated lesion of the arterial wall and protrudes into the lumen. Therefore, it can have clinical sequelae.

The more advanced lesion of atherosclerosis is sometimes called the complicated lesion. The fibrous cap becomes vascularized. In addition, the lipid-rich core enlarges and often calcifies. These lesions can be complex due to hemorrhage of the fibrous cap as well as its calcification. If the cap fissures or ruptures, an intense thrombogenic cascade can ensue that may lead to occlusive coronary disease.

Until recently, it was believed that the calcium in atherosclerotic plaques was simply calcium phosphate, which precipitated in a passive manner. Instead, it has been shown that the calcium in coronary arteries is in the form of calcium hydroxyapatite and is deposited in a process similar to that of active bone formation (11). Fitzpatrick et al. used undecalcified postmortem coronary arteries to study mineralization (12) and found that calcification was present in all atherosclerotic plaques. In addition, they identified a cell attachment protein (osteopontin), a protein associated with calcification (osteonectin) and a gamma-carboxylated protein that regulates mineralization (osteocalcin). Bostrom et al. identified bone morphogenic protein 2a in calcified atherosclerotic plaques (13). These studies show that calcification in atherosclerotic lesions is an active process, regulated in a manner similar to that of bone mineralization.

Coronary Artery Calcium-Imaging Techniques

Coronary artery calcification can be detected by multiple imaging modalities. Plain radiography, fluoroscopy, computed tomography, ultrasound and magnetic resonance imaging (MRI) have been used. Fluoroscopy and CT are the methods most commonly used today.

Chest radiography can detect coronary artery calcifications. However, it is limited by overlying shadows as well as by the amount and density of the calcifications. One study reported an accuracy rate of only 42% (14).

Fluoroscopy is frequently used to detect coronary calcifications, since it is a component of coronary angiography. Both conventional fluoroscopy and, more recently, digital subtraction fluoroscopy are being utilized. In a study of asymptomatic male air-crew members who underwent coronary angiography because of one or more abnormal screening tests, coronary artery calcification had a 66.3% sensitivity and a 77.6% specificity for predicting angiographically significant (greater than 50% diameter narrowing) stenosis (15). The authors concluded that the absence of fluoroscopically detectable coronary artery calcification indicated a low likelihood of significant coronary artery disease, while its presence raised the likelihood.

While fluoroscopy is relatively inexpensive and widely available, it does have disadvantages. One major limitation is that it is often unable to detect small calcium deposits. Agatston et al. (16) found that only 52% of calcium deposits seen on electron-beam CT (EBCT) could be detected fluoroscopically. The mean attenuation value for the EBCT-detected calcifications was +99 Hounsfield units (HU), whereas that for the fluoroscopically detected calcifications was +546 HU. This study demonstrated that only the larger, more heavily calcified deposits were detectable with fluoroscopy as compared with EBCT. Another disadvantage is its inability to provide a clear image in some patients with unusual body habitus, as well as in those with overlying anatomic structures and other cardiac calcifications (valve annuli, myocardial and pericardial calcifications). In addition, fluoroscopy is heavily dependent on the skill and experience of the operator as well as the number of views obtained.

CT is sensitive for detection of calcifications, due to its ability to differentiate calcium from adjacent soft tissues (Fig. 1). A study was performed comparing CT, fluoroscopy, and angiography in a group of patients with angina (17). CT revealed calcified plaques in 62% of patients with significant stenosis at angiography, compared to 35% detected with fluoroscopy. In a group without angina, CT found coronary calcification in only 4%, none of whom had significant stenoses at angiography. Overall, CT showed calcifications in 50% more vessels than did fluoroscopy. In this study, CT detected calcification in all patients in whom fluoroscopy detected calcified plaques and in all patients in whom angiography showed stenosis. In another study of patients with suspected coronary artery disease, CT showed a 65% sensitivity and an 87% specificity for coronary artery calcification (18). Of 108 patients with calcification detected by CT, 90% had significant stenosis (greater than 75% narrowing), whereas 80% of 121 patients with significant stenosis on angiography had calcification on CT.

The main disadvantage of conventional CT is its long scan time. This leads to motion artifacts, volume averaging and breathing misregistration. Helical CT has faster scan times, of approximately 1 sec. Faster scanning reduces the artifacts associated with conventional CT, but cardiac motion still blurs calcium deposits, and small calcifications may be missed (19). However, a recent study showed that images acquired with an electrocardiogram-gated subsecond helical scanner correlated well with those acquired by EBCT (20). In addition, Becker et al. reported that data acquired by EBCT correlated with that obtained by the newest generation of CT scanner, the multirow detector CT (21).

Electron-beam computed tomography (EBCT) is the main instrument involved in cardiac calcification imaging (Fig. 2). The physics of this new type of scanner is different from that of a helical scanner (22). With a helical scanner the x-ray source rotates around the patient while the detectors are stationary. An EBCT scanner has no moving parts. A high-energy electron beam originating from a structure behind the gantry is steered around the patient electronically and strikes a tungsten ring which encircles the patient. The resultant x-rays are focused onto detectors approximately 180° opposite. The major advantage of this technology is rapid scan times on the order of 100 milliseconds (increased temporal resolution compared to helical scanners). The main disadvantage is that fewer photons are used to produce an image. Thus, the images are less sharp (increased noise).

Ultrasound, frequently used to image the heart, is sensitive for the detection of calcification. Transthoracic echocardiography (TEE) is limited in usefulness for detection of coronary artery calcifications, due to poor external acoustic windows. While TEE can often identify the proximal coronary arteries (23, 24), it does not image the entire coronary tree well. Intravascular ultrasound (IVUS), a newer modality for evaluation of the coronary arteries, is most often used during coronary angiography. The ultrasound provides information about the vessel wall thickness and tissue characteristics. Calcification is depicted as a hyperechoic area with posterior shadowing; noncalcified fibrous plaques are hyperechoic without

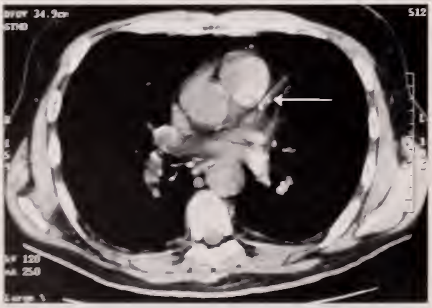

Fig. 1. Helical CT scan showing calcification (arrow) along the proximal left anterior descending artery (arrow).

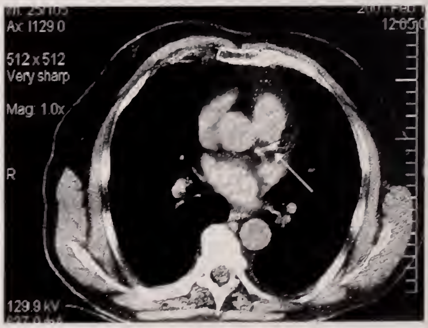

Fig. 2. Electron beam CT scan demonstrating calcification (arrow) in the left anterior descending artery (arrow).

associated shadowing (25). Recent studies (25, 26) comparing IVUS and angiography show angiography to be less sensitive at detecting calcification at the site of an atherosclerotic plaque.

The disadvantage of IVUS is that it is invasive and is, therefore, usually performed at the same time as selective coronary angiography. Also, because of the size of the catheters, it can only visualize the proximal coronary arteries. Therefore, it has a limited role in screening for coronary artery disease (CAD). Its importance lies in the fact that it can depict atherosclerotic lesions in patients with normal angiograms (27).

Magnetic resonance imaging does not excel in detecting small quantities of calcification, such as those found in early atherosclerotic plaques, and therefore plays little if any role in the early detection or screening of CAD.

Coronary Artery Calcium-Scoring Technique

In 1990 Agatston and colleagues published a report of a method of quantifying or scoring the amount of coronary artery calcification using EBCT (16). This EBCT study was electrocardiogram-gated with each slice triggered at 80% of the patient's R-R interval, so that images were obtained at the same point in diastole. Each image was obtained with 100-millisecond scan time and 3-millimeter slice thickness. Twenty slices were acquired in this study, although today 40 slices are usually acquired, to include the entire epicardial coronary system. Each slice was examined for calcium deposits. When a focus of calcium was detected, a region of interest was drawn around it. The area of the calcium deposit and its peak density were then determined. A deposit had to have a density measurement of at least +130 HU and an area of at least 1.0 mm^2. A density of 130 HU was chosen because this amount is well above the density of unenhanced myocardium and soft tissues (30–50 HU). The area measurement was used to try to discriminate noise from true calcium. An area of 1.0 mm^2 corresponds to at least 2 contiguous pixels at the usual scanning parameters. Noise usually comprises only one pixel. The calcium deposits that met these criteria were then scored. The Agatston score is a weighted score, calculated by multiplying the area of the calcification (in mm^2) by a factor determined by the peak density within the area of interest. A factor of 1 was used for densities from 131–199; 2 for 200–299; 3 for 300–399; and 4 for 400 or greater. The score for each calcification was determined and added to calculate the total calcium score for each coronary artery or for the entire epicardial arterial system. At about the same time, the Japanese developed a calcification scoring system using conventional CT, based on the length of calcifications (28), but it did not gain widespread acceptance.

Calcification and Coronary Artery Disease

As stated previously, it has been shown that calcification is associated with atherosclerotic plaque. The cardinal question remains, is calcified plaque associated with significant luminal stenosis? Mautner et al. conducted a study correlating EBCT-detected calcification and histologic plaque (29). They found that EBCT-detected calcification was present in 54% of coronary segments with stenosis of greater than 75%, in 41% of segments with 51–75% stenosis, in 23% of segments with 26–50% stenosis and in 6% of segments with 0–25% stenosis. Their data also showed that there was detectable calcification in 93% of segments with greater than 75% stenosis, but it was present in 20% of those with less than 50% stenosis and only 4% of those with less than 25% stenosis. It should be noted that this study used histologically determined stenosis of arteries, using the area of plaque central to the internal elastic lamina, and not the angiographic narrowing based on luminal diameter. Another study demonstrated that although calcified plaque is associated with atherosclerosis, the calcified plaque does not always correlate with the exact site of luminal stenosis (30, 31). In fact, some high-grade lesions and many smaller ones lack calcification altogether (29, 32). Rumberger et al. found that the total calcium area was roughly 20% of the total atherosclerotic plaque burden (32).

Coronary artery calcification is accepted as a marker of atherosclerosis. However, there is still controversy over what constitutes a vulnerable plaque. Some believe that calcification is an attempt by the body to protect weakened myocardium by strengthening the atherosclerotic plaque prone to rupture (33). The calcification may represent a stabilization attempt by the body to prevent plaque rupture. It has been shown that calcified areas are unlikely to be associated with sites of plaque rupture (34). However, the stiffened calcified area can induce stress at the junction of the calcified and noncalcified sections, a common site of plaque rupture (35). On the other hand, others believe that a mildly or moderately stenotic plaque is more likely to rupture and lead to a coronary event (36). The reasoning is that the presence of calcium implies the presence of unstable and vulnerable lipid-rich plaques. This correlates with Rumberger's finding that only 20% of a plaque is calcified (32).

Studies have also correlated EBCT-detected calcification with known CAD risk factors. Goel and colleagues found an increased prevalence of coronary calcification associated with diabetes, smoking, hypertension, and a history of chest pain or previous myocardial infarction in men and hypercholesterolemia and smoking in women (37). Wong et al. performed a similar study in asymptomatic subjects (38). They found a higher prevalence of calcification in men with hypertension, diabetes, smoking, hypercholesterolemia, infrequent exercise and obesity; in women the association only held with hypercholesterolemia. Guerci et al. compared calcium scores with conventional risk factors in a group undergoing coronary angiography for clinical indications (39). For significant obstructive coronary disease, the calcium score had a higher odds ratio than most other risk factors, such as lipid profile, hypertension, smoking history, diabetes, family history of CAD, age, and gender.

Age and gender have been the risk factors with the most interesting trends concerning coronary calcification. In a large study by Janowitz et al. (40), 1,898 men and women aged 20 – 80 years were studied using EBCT. Their data show that while the prevalence of coronary artery calcium increased with age, the prevalence of coronary artery calcium was lower in women compared to age-matched men until about the seventh decade. Moreover, the 10-year lag in the prevalence of calcification in women in comparison to men narrowed in the first decade after menopause. Therefore, EBCT-detected calcification seems to follow the epidemiological pattern of atherosclerosis.

Numerous studies have shown an association between coronary artery calcification and coronary artery disease, as proven angiographically. In Agatston's study (16), in which he described the scoring method, 584 patients underwent EBCT. Of these, 109 had coronary artery disease, as established by a history of myocardial infarction or more than 50% luminal stenosis on angiography. The other 475 patients had no history of CAD. Those with CAD had more calcified plaques compared to aged-matched individuals without CAD. A calcification score of 300 had a sensitivity of 74% and a specificity of 81% in the detection of obstructive CAD. The negative predictive value of a calcium score of zero was 98%. In another study (41), 100 patients aged 23 – 59 years were evaluated with EBCT and coronary angiography. Sensitivity and specificity for detecting calcified plaques in subjects with angiographically significant stenosis (greater than 50%) was 100% and 47%, respectively.

The largest multicenter study involved 710 subjects with symptoms of CAD and a mean age of 56 years (42). There were 456 men and 254 women. Each subject underwent both EBCT and coronary angiography. Significant stenosis was defined as narrowing greater than 50%. The sensitivity of the coronary calcium score in patients with significant stenosis was 95% (404 out of 427 patients). The specificity was 44% (124 out of 283 patients). The negative predictive value was 84%. As these studies show, there is high sensitivity for the association between significant CAD and detectable calcifications using EBCT. The specificity is low. This probably relates to the fact that only 20% of atherosclerotic plaque is calcified. However, the absence of calcification seems to indicate a lack of significant luminal stenosis. In a study of 150 patients, Stanford et al. found only one patient with a stenosis of greater than 50% and no coronary artery calcium (43).

Recently, He et al. studied a group of 3,895 mostly asymptomatic patients with EBCT (44), 411 of whom had myocardial single proton emission computed tomography (SPECT) studies shortly thereafter, i.e., within a median period of 17 days. No patient with a calcium score of less than 10 had an abnormal SPECT. On the other hand, 2.6% with a score of 11 – 100, 11.3% with a score of 101 – 399 and 46% with a score greater than 400 had a SPECT showing ischemia. They concluded that the calcium score can identify a high-risk group with silent myocardial ischemia within a low-risk population.

More recently, Raggi et al. studied the coronary calcium score as a predictor of unheralded myocardial infarction (45). They studied 632 asymptomatic patients as well as 172 patients who had an acute myocardial infarction with no previous manifestations of CAD. The asymptomatic group was followed for the development of myocardial infarction or cardiac death for approximately 32 months. The groups were compared using sex- and age-matched cardiac score percentiles. They found that 70% of patients who had a myocardial infarction or who died had coronary calcium scores greater than the 75th percentile.

Another important aspect of a test to detect early coronary artery disease is the ability to follow its progression or regression over time. Information on the reproducibility of coronary artery calcium scoring is not consistent. Janowitz and associates calculated calcium scores twice for plaques in 25 asymptomatic and symptomatic patients, 406 days apart (46). There was a 48% increase in the calcium score in the patients with proven obstructive CAD compared with 22% in the asymptomatic group. Also, the patients with proven CAD had 55 new calcified deposits versus 18 in the asymptomatic cohort. The authors concluded that coronary artery calcium scores could be used to follow the natural history of CAD. However, they did not take into account that the differences might be due to interscan measurement error. Another study showed that when a repeat EBCT scan was performed after the patient had gotten off the table and walked around the room, many small calcifications were not seen (47). Deposits of less than 2 mm^2 were missed up to 50% of the time. Other investigators have demonstrated that large increases in the calcium score are needed before the change can be attributed to disease progression rather than to measurement error (48–50). The variability between scans is usually due to misregistration resulting from patient motion. Increasing the slice thickness to 6 mm has been shown to decrease the interscan variability (50).

Calcification and Prognosis

It has been established that the coronary artery calcification score is an indicator of the overall atherosclerotic plaque burden (32). Furthermore, the greater the plaque burden, the more likely it is that one of the plaques may be unstable and lead to a cardiovascular event. The event data in turn (angina, myocardial infarction, need of coronary angioplasty or revascularization, and death) are essential to determining the clinical significance and utility of the coronary artery calcification score.

Detrano et al. conducted a study of survival in asymptomatic, high-risk subjects with coronary artery calcium detected at fluoroscopy (51). They followed 1,461 subjects with a greater than 10% risk of having a coronary event (defined as angina, documented myocardial infarction, myocardial revascularization, or death from coronary heart disease). At one year, events occurred in 5.4% of the subjects with coronary calcification versus 2.1% of those without calcium. One-vessel calcification had a risk of an event of 5.4%, two-vessel calcification had a risk of 5.6% and three-vessel calcification incurred a risk of 6.2%. They concluded that the presence of fluoroscopically detectable coronary artery calcification identified an increased risk of cardiac events in asymptomatic, high-risk subjects and that this risk was independent of the risk incurred by standard risk factors.

Several studies have been conducted utilizing EBCT-detected calcification and event outcomes. Detrano and colleagues also performed an EBCT study involving 491 patients with a mean age of 55 years who were referred for coronary angiography (52). There were 13 coronary-heart-disease-related deaths (12 sudden cardiac deaths and 1 fatal myocardial infarction) and 8 nonfatal myocardial infarctions during the 30 ± 13 month follow-up period. One patient in the first quartile had an event, 2 patients in the second quartile, 8 in the third, and 10 in the fourth. The odds ratio for cardiac events in patients with calcium scores above the 75th percentile versus those below the 35th percentile was calculated at 10.8. In addition, the event-free survival rate was significantly greater for patients with a calcium score below 100 than for those with scores above this level.

Arad and co-workers monitored 1,173 asymptomatic patients (mean age 53 years) with no known CAD for 19 months following an EBCT exam (53). Eighteen (18) subjects had 26 cardiovascular events: 1 death, 7 nonfatal myocardial infarctions, 9 coronary angioplasty procedures, 8 revascularization procedures and 1 nonhemorrhagic stroke. The coronary artery calcification scores were divided into three threshold groups: greater than 100, greater than 160, and greater than 680. The sensitivities for these groups were 89%, 89%, and 50% respectively. The specificities were 77%, 82%, and 95% respectively. The negative predictive values were greater than 99% for all groups. The odds ratios were 25.8, 35.4, and 20.0 respectively. This study has now been carried out for a total of 3.6 years of follow-up (54). The odds ratio for a baseline calcium score of greater than 160 remain significant at 23.

Agatston and associates studied 367 asymptomatic patients with a mean age of 52 years who were followed for 36–72 months (55). A total of 26 events occurred, consisting of the development of angina, myocardial infarction, or coronary angioplasty, or need for revascularization. The mean calcium score for those with an event was 399, while those without events had a mean score of 76. The authors also calculated an odds ratio of 6.9 for the development of symptomatic CAD for those with a calcium score of greater than 50 versus 2.7 for those with a score below 50.

Conclusion

Coronary artery calcification is intimately associated with atherosclerotic plaque. It can be detected with EBCT *in vivo* in a noninvasive manner, and the amount of calcification can be quantitated. This calcium score is related to the total atherosclerotic plaque burden within the coronary system. Whereas the total calcified area may represent roughly 20% of the overall plaque area, the calcified plaque does not necessarily correspond to the site of luminal stenosis in a patient with obstructive coronary artery disease. A negative or very low (0 – 10) calcification score generally excludes the possibility of significant coronary artery stenosis, but not the presence of an unstable atherosclerotic plaque that can lead to a cardiac event. Identifying patients early in the course of coronary artery disease would be a major public health advance, since multiple studies have shown benefit following the use of lipid-lowering agents in patients with known or asymptomatic CAD (56 – 59). The role of EBCT scanning as a screening tool to reduce the morbidity and mortality from CAD, the leading cause of death in the United States, has not been established. However, this technique is useful for evaluating patients with atypical chest pain syndromes. If the patient has no detectable calcium, the source of the chest pain is not likely to be due to CAD. If there is moderate-to-severe calcification present, then the patient can be scheduled for more traditional tests for cardiac ischemia. Another possible role for EBCT could be in following the progression or regression of CAD in patients on medical therapy (60). However, interscan measurement variability needs to be addressed before this can be a practical application.

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Nocturnal Asthma:

Mechanisms and Management

Gwen S. Skloot, M.D.

Abstract

Nocturnal asthma, defined as an exacerbation of asthma at night, is associated with increases in symptoms and need for medication, increased airway responsiveness and worsening of lung function. Nighttime worsening of asthma has been recognized since the 5th century A.D. and is believed to be quite common, affecting a majority of asthmatics. The mechanisms of nocturnal asthma are intimately related to circadian rhythms, which influence inflammatory cells and mediators, hormone levels and cholinergic tone. Patients with nocturnal asthma symptoms may have greater nighttime activation of inflammatory cells and mediators, lower levels of epinephrine and increased vagal tone. In addition, underlying differences in the glucocorticoid receptor and β-receptors in these patients may diminish their ability to respond to therapy. While sleep appears to play a role in the pathophysiology of nocturnal asthma, it is not essential to it. Selective timing of medication can increase its efficacy and reduce its toxicity. Available therapy includes inhaled and oral corticosteroids, sustained-release theophylline, long-acting β-agonists, leukotriene-modifying agents and anticholinergic medication. The definition, epidemiology, potential mechanisms and management of nocturnal asthma are discussed in this review.

Key Words: Nocturnal asthma, chronobiology, chronotherapy, inflammation.

Introduction and Epidemiology

Asthma is a chronic inflammatory disease of the airways, characterized by hyperresponsiveness to a variety of stimuli (1). It has long been recognized that asthma is worse at night. One of the earliest observations of a day-night pattern in asthma was made by Aurelianus Caelius in the 5th century A.D. (2). In the 1880s, Slater (2) wrote that "sleep favours asthma…spasm of the bronchial tubes is more prone to occur during the insensibility and lethargy of sleep than during the waking hours."

Nocturnal asthma is defined as a variable nighttime exacerbation of the underlying asthma condition associated with increases in symptoms and need for medication, increased airway responsiveness and/or worsening of lung function (3). Generally, a reduction in peak flow or forced expiratory volume in one second (FEV1) of at least 20% is implicit in this definition. Approximately two-thirds of asthmatics suffer from nighttime symptoms (4). In a large study by Turner-Warwick involving 8,000 asthmatics (5), 75% awakened one night per week, 64% awakened 3 nights per week and 39% had their sleep disturbed on a nightly basis. Interestingly, of the patients who self-characterized their asthma as mild, 26% had nightly awakenings. The frequency of nocturnal awakenings did not appear to be related to a specific medication or combination of medications. There was also no particular trigger factor associated with nocturnal asthma, but allergic triggers were generally more frequent in this population than in patients without evidence of nocturnal asthma. In a study by Robertson et al. (6), 53% of asthma deaths occurred during the nighttime hours. The prevalence of nocturnal asthma is most likely underestimated. A better understanding of the mechanisms and management of this entity seems warranted.

Nocturnal Asthma and Chronobiology

The principles of chronobiology provide a framework for understanding nocturnal asthma.

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Chronobiology is the study of biological rhythms and their mechanisms (7). Every biological rhythm has a periodicity. Circadian rhythms have a periodicity of about 24 hours. It is well known that circadian rhythms influence disease processes and physiological events. For example, most myocardial infarctions occur in the early hours of the morning. Lung function (e.g., peak expiratory flow rate or FEV_1) is usually highest at 4 PM and lowest at 4 AM (7). The latter time is generally when asthma symptoms are most prevalent. Dethlefsen and Repges (8) studied a population of more than 3,000 patients (mainly asthmatics) and demonstrated that more than 90% of their dyspneic episodes occurred during the nighttime hours (Fig. 1). Clark and Hetzel (9) showed that diurnal variation in lung function exists in both healthy and asthmatic subjects (Fig. 2). However, the amplitude of variation is much greater in asthmatics, due to the greater dip in their peak expiratory flow rate at 4 in the morning. These investigators found that, on average, the diurnal variation was 8% in healthy subjects and 51% in asthmatics. A large circadian variation has been shown to precede sudden death and may or may not be reduced by anti-inflammatory therapy (10). In addition to the circadian variation in lung function in asthmatics, there is also a circadian variation in bronchial hyperresponsiveness (11). This variation in bronchial hyperresponsiveness is accentuated in subjects with nocturnal asthma. Those with nighttime symptoms have an eightfold increase in bronchial reactivity overnight, as opposed to a twofold increase in reactivity in subjects without nocturnal asthma.

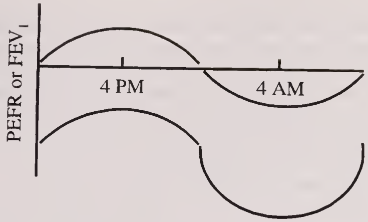

Fig. 2. Diurnal variation in lung function in healthy (top curve) and asthmatic (bottom curve) subjects. PEFR = peak expiratory flow rate; FEV_1 = forced expiratory volume in one second. Adapted, with permission, from reference 12.

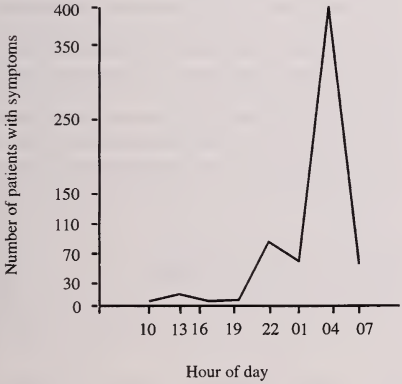

Fig. 1. Timing of dyspneic episodes in asthma. Hour of day is shown in military time. Asthma symptoms occurred most often between 2200 and 0700 hours, with a peak occurrence at 0400. Adapted, with permission, from reference 8.

Potential Mechanisms of Nocturnal Asthma

Fig. 3 shows an overview of the potential mechanisms of nocturnal asthma and suggests that there is a complex interaction of many factors (12). These factors include a circadian variation in inflammatory cells and mediators, hormone levels, and vagal tone, all of which can enhance bronchial reactivity. Upper airway diseases such as chronic sinusitis and obstructive sleep apnea can modulate several of these factors.

Inflammatory Cells and Mediators

Approximately 40% of asthmatics exhibit a late phase reaction when exposed to allergen

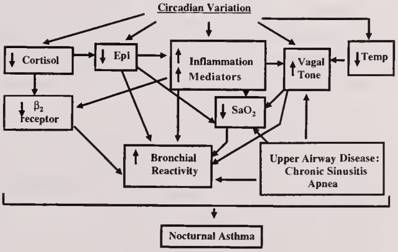

Fig. 3. Overview of potential mechanisms of nocturnal asthma. Temp = temperature; Epi = epinephrine; SaO_2 = oxygen saturation. Mediators: A variety of substances released from mast cells, eosinophils, lymphocytes, etc. Adapted, with permission, from reference 12.

(13). This reaction, due to airway inflammatory changes, is characterized by asthma symptoms which begin approximately 4 hours after the initial exposure and can last for 24 hours. The late phase is distinct from the early reaction, which generally resolves within one hour following exposure, and is due mostly to airway smooth muscle spasm (14).

Mohiuddin and Martin (15) studied the circadian basis of the late asthmatic response, hypothesizing that there might be a circadian variation in occurrence and severity. They challenged 10 asthmatic subjects with inhaled allergen at two time points, 8 AM and 8 PM. As can be seen in Fig. 4, all 10 individuals had an early phase reaction regardless of the time of challenge, but significantly more subjects had a late phase when challenged nocturnally ($p<0.05$). This late phase was more severe, based on the reduction in lung function, tended to last longer and was followed by increased reactivity to methacholine at 24 hours after challenge.

In 1991, Martin et al. (16) extended this work by hypothesizing that inflammatory cells would be increased in bronchoalveolar fluid at night in patients with nocturnal asthma as opposed to those without nighttime symptoms. Seven patients with nocturnal asthma and 7 with non-nocturnal asthma underwent bronchoscopy at 4 PM and 4 AM. As shown in Table 1, the nocturnal asthma group manifested significant circadian variation in inflammatory cells, with increased total cells, neutrophils and eosinophils at 4 AM vs. 4 PM. These subjects also had an increase in most cellular elements compared to non-nocturnal asthmatics at 4 AM. Cell counts were not significantly different in the two groups at 4 PM. For all subjects, the overnight reduction in peak expiratory flow rate correlated with the overnight change in neutrophils and eosinophils.

Wenzel et al. (17) studied the contribution of leukotrienes to nocturnal asthma by measuring their levels at night in both bronchoalveolar lavage and urine, in asthmatics with nighttime worsening and in healthy controls. Both bronchoalveolar and urinary leukotrienes were increased in the nocturnal asthma group. Leukotriene B_4 levels correlated significantly with the nocturnal fall in FEV_1.

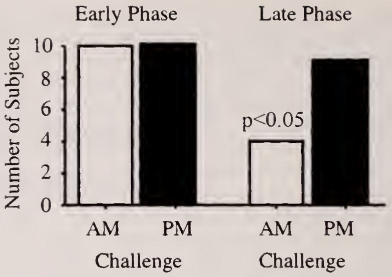

Fig. 4. Circadian variation exists in the late asthmatic response to allergen but not in the early response. Reproduced, with permission, from reference 15.

The preceding studies suggest that worsening of asthma at night may relate, at least in part, to an increase in the inflammatory cells and mediators in the lung during the nighttime hours. Kraft and co-workers (18) investigated the site of inflammation in the lung, hypothesizing that the greatest circadian changes in eosinophilic airway inflammation would occur distally. This group performed fiberoptic bronchoscopy with both endobronchial (proximal) and transbronchial (distal) biopsy at 4 AM and 4 PM, in 11 subjects with nocturnal asthma and 10 with non-nocturnal asthma. Only the nocturnal asthma group had a greater number of eosinophils (per volume) at 4 AM than at 4 PM by transbronchial biopsy. The number of eosinophils obtained by endobronchial biopsy was low in both groups (regardless of time), as though these cells were migrating more distally in the lung. Alveolar tissue eosinophils corre-

TABLE 1

Bronchoalveolar Lavage Cytology in Patients With and Without Nocturnal Asthma

Cells	Non-nocturnal Asthma		Nocturnal Asthma	
(x 10^4/mL)	4 PM	4 AM	4 PM	4 AM
Total White Cells	18.3 ± 4.2	16.4 ± 2.0	24.0 ± 7.0	41.1 ± 9.9*†
Neutrophils	0.22 ± 0.06	0.2 ± 0.07	1.1 ± 0.6	3.7 ± 1.5*†
Eosinophils	0.29 ± 0.08	0.22 ± 0.07	0.5 ± 0.1	1.7 ± 0.7*†
Lymphocytes	2.4 ± 0.4	3.1 ± 0.7	7.0 ± 2.0	10.8 ± 3.6†

*$p<0.05$ within a group between 4 PM and 4 AM. $^{\dagger}p<0.05$ between groups at 4 AM. Adapted, with permission, from reference 16.

lated with the nocturnal decrement in lung function. This study thus supports the idea that the alveolar tissue is an important site of inflammation in nocturnal asthma.

More recently, Kraft et al. (19) evaluated the glucocorticoid receptor binding affinity and steroid responsiveness in subjects with nocturnal asthma at 4 PM and 4 AM, using radioligand binding and lymphocyte proliferation studies. They found that, compared with non-nocturnal asthmatics and healthy controls, those asthmatics with nighttime symptoms had a reduced steroid receptor binding affinity at 4 AM, which correlated with the decreased FEV1 at the same time. The nocturnal asthma group also demonstrated a diminished response to steroid treatment at 4 AM. These data indicated that patients with nocturnal asthma may have some unique features to their disease. For example, it has been proposed that differences in the cytokine milieu in these patients might lead to the observed alterations in the glucocorticoid receptor (20).

Humoral Changes

It is suggested that humoral changes may account for the phenomenon of worsening of asthma at night. Barnes and colleagues (21) investigated the idea that circadian rhythm may be important in the changes in airway tone in 5 nocturnal asthmatics and 5 healthy controls. Plasma hormone levels were measured at various times in both groups, and the effect of epinephrine infusion on lung function and on histamine level was assessed in the asthmatics. Interestingly, in the asthmatic cohort, the nadir in peak flow (4 AM) was associated with the nadir of the epinephrine level and the peak of the histamine level. Infusion of physiologic doses of epinephrine in these subjects diminished the overnight decline in lung function and also decreased the histamine level. The authors speculated that circulating epinephrine may act directly on β-receptors on bronchial smooth muscle or indirectly on β-receptors on mast cells to inhibit release of histamine. Other investigators (22), however, have not confirmed the finding by Barnes et al. of a nocturnal rise in plasma histamine level in patients with evidence of nighttime asthma.

Cholinergic Tone/β-Agonist Function

It is known that increased vagal tone at night affects the heart. This change in vagal tone may also impact on bronchomotor tone (23, 24). Morrison et al. (25) hypothesized that the parasympathetic nervous system may play a role in nocturnal asthma. They performed a placebo-controlled study of the effect of intravenous atropine on peak expiratory flow at 4 AM and 4 PM, in 10 subjects with nocturnal asthma. Atropine increased peak expiratory flow at both times, but the increase was significantly greater at 4 AM (Fig. 5). The circadian variation which existed with placebo was almost completely abolished after atropine. These results support the idea that the increased vagal tone at night may affect some patients with nocturnal asthma. In particular, patients with both asthma and obstructive sleep apnea syndrome may fall into this category, since obstructive sleep apnea and snoring can both increase vagal tone (26). It has been suggested that snoring is more prevalent in the asthmatic population (27), perhaps due to allergic rhinitis. Another potential contributing factor to nocturnal asthma, based on increased cholinergic tone, is gastroesophageal reflux disease (GERD) (28). The most widely accepted theory for this association is that acid reflux may stimulate vagal receptors in the lower esophagus, leading to reflex bronchoconstriction. Some authors, however, have minimized the role of GERD in nocturnal asthma. Tan and colleagues (29) studied the effect of esophageal acid on lower airway resistance in sleeping patients with nocturnal asthma (between the hours of 11 PM and 6 AM). Hydrochloric acid (0.1 N) was instilled via a nasogastric tube at a rate of 3 mL/min; a pH probe located above the gastroesophageal junction was used to confirm the presence of an acidic pH. Lower airway resistance was calculated from measured esophageal and supraglottic pressures, respiratory flow rates and tidal volumes. The authors found no change in airway resistance relative to periods of intraesophageal acid. A full discussion of this controversy exceeds the scope of this review.

In a pharmacological study by Szefler and associates (30), the possibility of a circadian variation in leukocyte β_2-adrenergic receptor density and function was examined in 7 patients with nocturnal asthma, 10 with non-nocturnal asthma and 10 normal controls. This group found that the number and physiologic function of β_2-receptors was significantly decreased at 4 AM vs. 4 PM in patients with nocturnal asthma, compared to either of the other two cohorts. More recent work (31) has demonstrated that this phenotypic downregulation of β_2-receptors can be explained by a specific polymorphism in the genetic coding block of the receptor (substi-

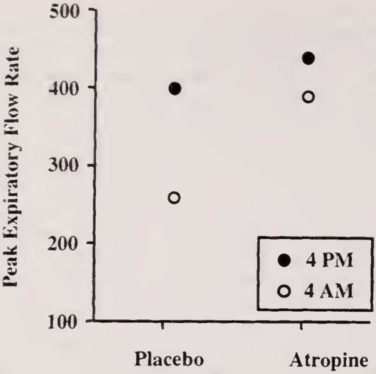

Fig. 5. Increase in peak expiratory flow rate with intravenous atropine versus placebo at 4 AM ($p<0.0001$) and 4 PM ($p<0.04$) in subjects with nocturnal asthma. The circadian variation in peak expiratory flow rate was significantly diminished after atropine ($p<0.01$). Adapted, with permission, from reference 25.

tution of glycine for arginine at position 16). This polymorphism is more frequent in patients with nocturnal asthma as well as in those with more severe asthma.

The Role of Sleep in Nocturnal Asthma

The changes which characterize nocturnal asthma have been related not only to circadian events but also to sleep. Clark and Hetzel (9) studied shift workers with asthma and found that the worsening of their disease was always linked to the sleep cycle, regardless of the time of day. Subsequently, this same group repudiated their own findings (32). In 1989, Ballard et al. (33) measured airway resistance in patients with nocturnal asthma, from midnight to 6 AM on one night when the patients were kept awake and on another night when they were asleep. On both occasions, airway resistance was noted to increase; however, the increase was twofold greater when the patients slept during the study period. Other related studies have looked at the role of supine posture and of the consequent decrease in lung volume in nocturnal asthma, but most have dismissed these factors as irrelevant (34, 35). Work by Irvin and colleagues (35) suggested that the airway and parenchyma may become "uncoupled" during sleep in patients with nocturnal asthma. Normally, the airway wall is tethered to the surrounding lung tissue or parenchyma, so that the two are interdependent. It is this interdependence which explains the normal hyperbolic relationship between lung volume and airway resistance; that is, as lung volume increases, airway resistance falls. In Irvin's patients with nocturnal asthma, increasing lung volume at night during sleep did not lower airway resistance as anticipated. The authors suggest that the airway and parenchyma may become "uncoupled" during sleep in patients with nocturnal asthma, as a result of alveolar inflammation and additional neural influences.

Management of Nocturnal Asthma: Chronotherapy

Chronotherapy is based on the importance of biologic rhythms in the pathophysiology of medical conditions and uses the timing of medications to provide maximal efficacy and minimal toxicity (7). The standard dosing schedule of certain asthma medications already takes into account the known diurnal variation of symptoms, while in other cases, specifically timed regimens need to be ordered by the prescribing physicians.

Multiple investigations have examined the role of chronotherapy in administration of corticosteroids. In 1983, Reinberg et al. (36) performed a double-blind, placebo-controlled, randomized crossover study of 8 asthmatics given oral steroids in divided doses at 8 AM and at 3 PM or 3 PM and at 8 PM, over 8 days. Their results demonstrated more effective control of asthma symptoms and enhanced peak flow with the 8 AM and 3 PM schedule. Of note, the patients were not selected based on established criteria for nocturnal asthma. Almost a decade later, Beam and associates (37) examined the effect of a single dose of prednisone delivered at one of 3 specific times (8 AM, 3 PM or 8 PM) on asthma outcomes. The study was double blinded and placebo-controlled, with a crossover arm, and was directed at patients with nocturnal asthma. Only the 3 PM dose of prednisone resulted in overnight spirometric improvement (Fig. 6) and significant reduction in the number of all cell types ($p<0.05$) in the 4 AM bronchoalveolar lavage cytology. The circadian variation in lung function associated with the afternoon dose of prednisone approached that expected in normal, nonasthmatic subjects. Another study looked at the effect of chronotherapy using inhaled steroids. Pincus et al. (38) evaluated 30 asthmatics and demonstrated that single daily administration of inhaled triamcinolone at 3 PM produced similar improvement in lung function, bronchial hyperresponsiveness and β-agonist use compared to a standard regimen of triamcinoline given four times daily without any increase in systemic effects. These studies support the idea that chronotherapy should play a role in the judicious use of corticosteroids for nocturnal asthma and that 3 PM is the most effective time of administration.

Evidence suggests that there is also a time dependence to the adverse effects of corticosteroids, since circadian variability exists for risk of adrenal suppression within a 24-hour dosing schedule (7). Maximum inhibition of adrenal gland function occurs with a regimen dosed at the end of the activity cycle and during sleep. Minimum inhibition occurs during the morning and early afternoon. At high enough doses of corticosteroids, the circadian variation in adrenal gland function may be overridden, so that suppression can occur with all regimens.

Although theophylline preparations have generally fallen out of favor for the treatment of asthma, they may be useful in the treatment of nocturnal asthma when administered at specific times in relation to the onset of symptoms. Numerous possible mechanisms of action have been proposed for theophylline, including an anti-inflammatory one. In support of this idea, Jarjour (39) demonstrated that nocturnal administration of theophylline increased the tolerance to inhaled antigen and diminished the severity of the late asthmatic response. Martin et al. (40) conducted a study involving 16 subjects with nocturnal asthma, randomized to receive either a once-daily preparation of theophylline at dinnertime or conventional twice-daily dosing for 5 days prior to crossover. The single dose regimen resulted in a higher nocturnal serum theophylline concentration and an improved morning FEV_1. The higher daytime serum theophylline level in the conventionally treated group was not associated with an increase in daytime lung function. This study indicated that time-related dosing of theophylline yields superior responses compared to a conventional dosing schedule.

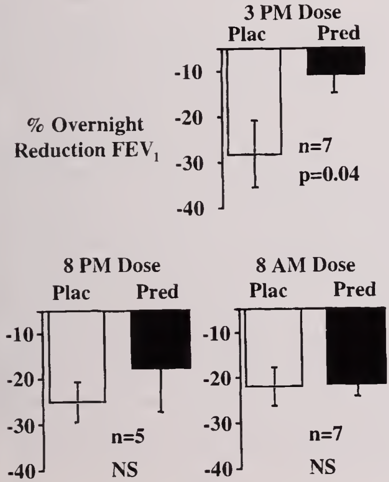

Fig. 6. The effect of the timing of oral corticosteroids on the percent overnight reduction in FEV_1 in subjects with nocturnal asthma. Plac = placebo, Pred = prednisone. Adapted, with permission, from reference 37.

One of the concerns regarding use of theophylline has been its suspected effect on sleep. Martin found no difference in polysomnographic evaluation of his asthmatic population (40) at a higher nighttime serum theophylline concentration. However, an earlier study by Rhind et al. (41) suggested that theophylline may impair sleep quality in asthmatics. The issue is complicated by the fact that, since airway dysfunction itself affects sleep, the secondary effect of theophylline may be difficult to interpret.

Several studies have examined the role of long-acting β-agonists in the treatment of nocturnal asthma. These medications incorporate chronotherapeutic principles into their dosing schedule. Fitzpatrick et al. (42) performed a randomized, double-blind, placebo-controlled crossover study evaluating two different doses of salmeterol (50 and 100 μg) in 20 patients with nocturnal asthma. Only the 50 μg dose significantly improved overnight peak expiratory flow and quality of sleep. It is likely that at higher doses, sleep is disrupted due to central nervous system absorption and stimulation. A subsequent investigation by Selby et al. (43) focused on a head-to-head comparison of inhaled salmeterol and oral sustained-release theophylline, using a double-blind, crossover design in 15 patients with nocturnal asthma. There were no major differences detected between the two regimens in terms of symptoms, pulmonary function and side effects. There was a small benefit in sleep quality with salmeterol. The largest study involving long-acting β-agonists enrolled 474 subjects with nocturnal asthma in a randomized, double-blind, placebo-controlled, multicenter clinical trial, to evaluate the effect of inhaled salmeterol on asthma outcomes (44). After 12 weeks of therapy, salmeterol significantly improved lung function (both

FEV_1 and peak expiratory flow rates), increased the percent of symptom-free days and nights, and decreased supplemental albuterol use.

Wenzel's study on the role of leukotrienes in nocturnal asthma (17) also had a therapeutic arm. Twelve subjects with nocturnal asthma were given zileuton, a 5-lipoxygenase inhibitor, in a randomized, double-blind, placebo-controlled fashion. Zileuton decreased both bronchoalveolar lavage and urinary leukotrienes. Nocturnal FEV_1 also demonstrated a trend toward improvement ($p = 0.086$). These changes were associated with significant reductions in 4 AM eosinophilia (fluid as well as blood). Newer leukotriene-modifying agents such as montelukast are administered at bedtime, with chronotherapeutic strategies in mind.

Since vagal tone is increased at night, anticholinergic therapy is more effective for control of nocturnal asthma symptoms than for daytime symptoms. Availability of longer-acting anticholinergic medications should be particularly helpful in this regard. Use of chronotherapy for agents such as cromolyn and nedocromil is not well understood.

Although there are multiple studies on chronotherapy for the treatment of nocturnal asthma, there are few overall guidelines with respect to when this therapy should be initiated. General strategies should include considering selective timing of a drug as an alternative to increasing its dose or adding another agent to attain control of asthma symptoms. The National Heart, Lung and Blood Institute has stratified asthma severity as mild, moderate and severe (45). The frequency of nocturnal awakenings is included in this characterization. For mild persistent asthma, inhaled corticosteroids dosed in the routine fashion should, over time, reduce airway inflammation and alleviate nocturnal asthma symptoms. Timed dosing may thus be more relevant for the moderate or severe asthmatic. Certainly, whenever an oral corticosteroid is required for an asthma exacerbation in a patient with nocturnal awakenings, there is evidence to support 3 PM administration. Anticholinergic medication should be considered as a nighttime rescue medication for all asthmatics. These and other recommendations for a chronotherapeutic approach to nocturnal asthma are summarized in Table 2.

Indirect therapy for nocturnal asthma is also important. Environmental control measures are essential and should focus on limiting the patient's exposure to allergens. Removal of pets from the bedroom, use of mattress and pillow covers, and carpet-free floors are some examples of helpful changes. Allergic rhinitis most likely demonstrates circadian variability as well (4) and should be treated with anti-inflammatory medications. Finally, since the obstructive sleep apnea syndrome and snoring can increase vagal tone and nocturnal bronchoconstriction, these entities should be diagnosed and treated appropriately. Guilleminault (26) has demonstrated that continuous positive airway pressure in a group of patients with concomitant asthma and obstructive sleep apnea syndrome (OSAS) improved both conditions.

TABLE 2

A Chronotherapeutic Approach to Nocturnal Asthma

AM	3 PM	6–7 PM	qHS
LA-β-agonist	Oral	SR-theophylline corticosteroid	Leukotriene modifier LA-β-agonist Anti-cholinergic

qHS = at bedtime; LA = long-acting; SR = sustained-release.

Summary

Nocturnal asthma is defined as an exacerbation of the underlying asthma condition at night, with usual peak flow variability of at least 20%. It is relatively common, affecting approximately two-thirds of asthmatics. The underlying mechanism likely involves endogenous circadian rhythms acting on the hyperreactive bronchi of people with asthma. Sleep seems to have a contributory role. Although patients with more severe asthma often have nighttime symptoms, nocturnal asthma may have some unique features. Circadian activation of inflammatory cells and mediators may occur to a greater degree in these individuals. A chronotherapeutic approach, in which corticosteroids, long-acting β-agonists, slow-release theophylline, leukotriene modifiers and anticholinergic medication are administered at specified times during the day, may enhance response to therapy. An increased understanding of circadian rhythms and their impact on nocturnal asthma should ultimately lead to the development of novel therapeutic strategies.

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Dean's Lecture

Sperm Receptors and Fertilization in Mammals

Paul M. Wassarman, Ph.D.

Abstract

During fertilization in mammals, sperm must first bind in a species-specific manner to the egg's thick extracellular coat, the zona pellucida. They then undergo a form of cellular exocytosis, the acrosome reaction. ZP3, one of three zona pellucida glycoproteins, serves as a structural glycoprotein, a sperm receptor, and an acrosome reaction-inducer. The latter two functions are mediated, at least in part, by ZP3 oligosaccharides. ZP3 is unique to mammalian eggs, from mice to humans, although related glycoproteins are found in vitelline envelopes of virtually all non-mammalian eggs, from fish to birds. Furthermore, the "zona domain" of zona pellucida glycoproteins, a characteristic ~260 amino acid-long region, is present in many (glyco)proteins with various functions in both vertebrates and invertebrates. It is tempting to suggest that egg-coat glycoproteins have evolved from solely structural components of certain non-mammalian egg vitelline envelopes into sperm receptors and acrosome reaction-inducers of the mammalian egg zona pellucida.

Key Words: Sperm receptors, fertilization, ZP3 glycoprotein, acrosome reaction.

Introduction

Infertility afflicts tens of millions of adult men and women worldwide. Although not recognized as a disease, it can be an extremely unpleasant burden for those individuals and couples affected by it. While *in vitro* fertilization (IVF) offers a means of circumventing many causes of infertility, it is not a universal solution to the problem, since there are numerous causes of infertility.

For more than twenty years, my laboratory has focused its efforts on one particular aspect of fertilization in mammals, the species-specific binding of free-swimming sperm to ovulated eggs. The failure of sperm to bind to ovulated eggs is frequently a cause of infertility among mammals. Our research is concerned primarily with the thick extracellular coat that surrounds all mammalian eggs, the zona pellucida (ZP). During the fertilization process, sperm must first bind to and then penetrate the ZP in order to reach and fuse with the egg plasma membrane (Fig. 1). In essence, the ZP serves as a "gate-keeper," to regulate sperm

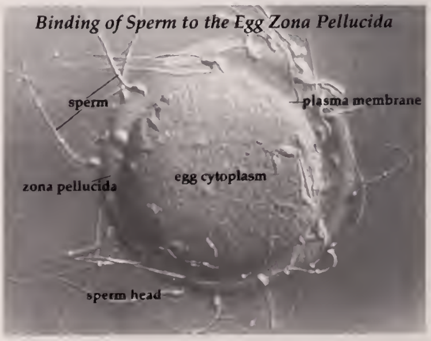

Fig. 1. Binding of sperm to the egg ZP. Light photomicrograph (Nomarski differential interference contrast) of mouse sperm bound to the ZP of an unfertilized mouse egg *in vitro*. (magnification ~600X).

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binding. In general, the ZP permits binding of sperm only when a sperm and an egg come from the same species ("species-specific binding"). Furthermore, once an egg has been fertilized, changes in the ZP eliminate binding of sperm, as part of the block to polyspermy. These and other features of the egg ZP strongly suggest that the ZP contains receptors ("sperm receptors") that need to be recognized by free-swimming sperm in order for them to bind to ovulated eggs in a species-specific manner (1, 2).

Twenty years ago it was already known that the mouse egg ZP possesses a sperm-receptor-like activity (3). For example, brief incubation of solubilized mouse egg ZP with mouse sperm prevented the sperm from binding to ovulated eggs. This was attributed to binding of sperm receptors present in the solubilized ZP preparations to these sperm, thereby inhibiting sperm from binding to eggs. On the other hand, solubilized ZP from either fertilized mouse eggs or preimplantation embryos had no effect on sperm binding. These, as well as other observations, prompted us, in 1977, to attempt to isolate the mouse sperm receptor and to characterize it. The following account summarizes our progress to date and suggests some areas of future research interest.

Fertilization in Mice

The final steps of mammalian oogenesis and spermatogenesis prepare eggs and sperm, respectively, for fertilization. During ovulation, fully grown oocytes from antral follicles undergo meiotic maturation and become unfertilized eggs prepared to interact with sperm. Similarly, following deposition into and migration up the female reproductive tract, sperm undergo capacitation, a process that enables them to bind to eggs and undergo the acrosome reaction (AR). Meiotic maturation of oocytes and capacitation of sperm set gametes off on a path that leads to either formation of a viable zygote or degeneration ("death") of the cells.

Typically, very few ovulated eggs are found in oviducts of females (mice, ~10). Similarly, relatively few sperm are found at the site of fertilization (mice, ~125) as compared to the number of sperm deposited into the female reproductive tract (mice, ~10^7). Only a very low percentage of ejaculated sperm ever make their way to the site(s) of unfertilized eggs in the oviduct. Whether binding of sperm to eggs occurs due to a chance encounter of gametes in the oviduct or is promoted by a chemical gradient stimulus ("sperm chemotaxis"), as found with many non-mammalian species, remains to be resolved conclusively.

Among mammals, the process of union of germ cells includes several steps that take place in an unvarying order. It begins in the oviduct with binding of free-swimming sperm to the ovulated egg ZP and ends a short time later (~1–2 hr after combining gametes *in vitro*) with fusion of egg and sperm plasma membranes to form a single activated cell, the zygote. Along the way, several recognizable events take place, including the sperm AR (a form of cellular exocytosis), penetration of the egg ZP by the sperm, and the egg cortical reaction and zona reaction (Fig. 2). The latter results in alteration of the ZP (so-called secondary block to polyspermy), such that free-swimming sperm are unable to bind to the ZP of fertilized eggs or preimplantation embryos.

Does mammalian fertilization exhibit any species specificity? It is well known that interspecific hybrids of certain mammals are viable. However, evidence from *in vitro* fertilization experiments strongly suggests that there are, indeed, barriers to interspecific fertilization and that the egg ZP serves as a major barrier. The ZP can interfere with interspecific fertilization by failing to permit the initial binding of sperm to eggs, induction of the AR, or penetration of bound sperm through the extracellular coat. Although the restrictions on binding are not ab-

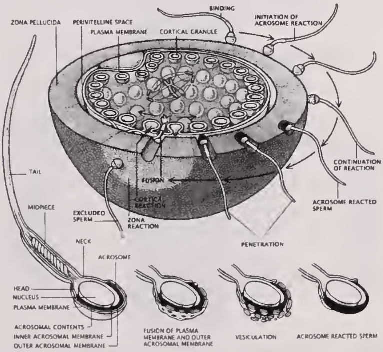
BINDING
INITIATION OF ACROSOME REACTION
ZONA PELLUCIDA
PERIVITELLINE SPACE
PLASMA MEMBRANE
CORTICAL GRANULE
TAIL
FUSION
CORTICAL REACTION
CONTINUATION OF REACTION
ACROSOME REACTED SPERM
MIDPIECE
EXCLUDED SPERM
ZONA REACTION
NECK
ACROSOME
PENETRATION
HEAD
NUCLEUS
PLASMA MEMBRANE
ACROSOMAL CONTENTS
INNER ACROSOMAL MEMBRANE
OUTER ACROSOMAL MEMBRANE
FUSION OF PLASMA MEMBRANE AND OUTER ACROSOMAL MEMBRANE
VESICULATION
ACROSOME REACTED SPERM

Fig. 2. Diagrammatic representation of the fertilization pathway in mice. Depicted are binding of acrosome-intact sperm to the unfertilized egg ZP; initiation of the acrosome reaction; penetration of the egg ZP by acrosome-reacted sperm; fusion of sperm and egg plasma membranes to produce a zygote; and initiation of the cortical and zona reactions.

solute, they provide for a relatively high degree of species-specific fertilization *in vitro*. Notably, removal of the ZP from unfertilized mammalian eggs, thereby exposing egg plasma membrane directly to acrosome-reacted sperm, eliminates the barrier to interspecific fertilization *in vitro* for many, but not all, mammals.

Nature of the Mouse Sperm Receptor, mZP3

The mouse sperm receptor is an ~83 kDa M_r ZP glycoprotein, called mZP3 (4–6). It is one of three glycoproteins, mZP1–3, that constitute the egg ZP (Fig. 3) (7). mZP3 consists of a polypeptide backbone to which asparagine- (N-) linked and serine/threonine- (O-) linked oligosaccharides are covalently attached. mZP3 polypeptide is synthesized as a ~44 kDa M_r species (424 amino acids); however, a signal sequence at its N-terminus (22 amino acids) and a fragment at its C-terminus (71 amino acids) are removed prior to incorporation of nascent mZP3 into the ZP (8–10). Approximately 260 amino acids of mZP3, which includes eight conserved cysteine residues, constitute a so-called "zona domain" (11), and this domain is present in mZP1 and mZP2 as well. A zona domain is present in all ZP glycoproteins, from mice to human beings, and is present at the C-terminus of many other (glyco)proteins found in both vertebrates and invertebrates (e.g., tectorin-β, uromodulin, ebnerin, cuticlin [*C. elegans*], and dumpy [*Drosophila*]) (12).

Of the three glycoproteins in the mouse egg ZP, only purified mZP3 binds exclusively to heads of acrosome-intact sperm, thereby preventing sperm from binding to ovulated eggs *in vitro* (4, 5, 13). Even at nanomolar concentrations, purified, unfertilized egg mZP3 is a very effective inhibitor of sperm binding (Fig. 4). On the other hand, at similar concentrations, mZP3 from fertilized eggs or early embryos has no effect on binding of sperm to eggs *in vitro*. This is consistent with the failure of free-swimming sperm to bind to the ZP of fertilized eggs and preimplantation embryos. It can be concluded from these and other observations that, as a consequence of the "zona reaction" shortly after fertilization, mZP3 is altered such that free-swimming sperm can no longer recognize and bind to the glycoprotein.

Molecular Basis of mZP3 Sperm Receptor Activity

Interestingly, the ability of mZP3 to act as a sperm receptor *in vitro* is not significantly affected by high temperatures, detergents, denat-

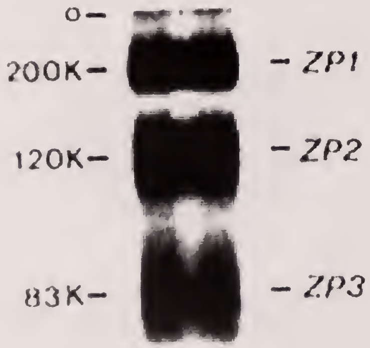

Fig. 3. Electrophoretic separation of mZP1, mZP2, and mZP3. Shown are the positions and molecular weights of radiolabeled ZP glycoproteins following one-dimensional sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) under non-reducing conditions and autoradiography. Note the breadth of the individual bands, reflecting heterogeneous—and O-linked glycosylation of unique polypeptides.

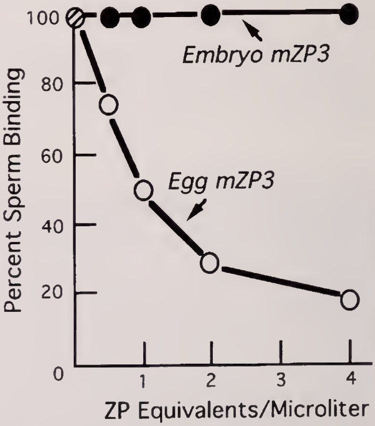

Fig. 4. Inhibition of sperm binding to eggs in the presence of purified egg mZP3 *in vitro*. Binding of mouse sperm to eggs was examined in the absence of mZP3 (hatched circle) and in the presence of either purified egg mZP3 (open circles) or two-cell embryo mZP3 (closed circles) at several concentrations. Note that egg mZP3 is a very effective inhibitor at nanomolar concentrations, whereas embryo mZP3 is inactive as an inhibitor at comparable concentrations.

urants, reducing agents, or limited proteolysis (14). Acrosome-intact sperm even bind to glass beads to which egg mZP3 is covalently linked (15). Apparently, mZP3 bioactivity is not dependent on the extent of glycosylation of its polypeptide or on sulfation and sialylation of its oligosaccharides (16). Even after extensive proteolysis of mZP3, the small glycopeptides produced retain activity as sperm receptors, although higher than usual concentrations are required (5, 17, 18). These observations suggest that mZP3 polypeptide does not play a direct role in sperm receptor function. However, there is considerable information to suggest that mZP3 oligosaccharides do play a direct role in sperm receptor function.

Chemical or enzymatic removal of all mZP3 oligosaccharides results in complete inactivation of the glycoprotein as a sperm receptor. Furthermore, O-linked oligosaccharides recovered from mZP3 by mild alkaline hydrolysis under reducing conditions (18–20) and certain O-linked-related oligosaccharides (21, 22) inhibit binding of sperm to eggs *in vitro* at micromolar concentrations. Results of some of these studies suggest that galactose, N-acetylglucosamine, and/or fucose are essential sugars for sperm binding. Collectively, these observations suggest that species-specific binding of sperm to eggs in mammals is a carbohydrate-mediated event. On the other hand, the identity of individual sugars that are recognized by sperm on mZP3 remains an unresolved and controversial issue (6).

To locate essential O-linked oligosaccharides on mZP3 polypeptide, limited proteolysis (23, 24), exon swapping (25) and site-directed mutagenesis (25, 26) were utilized. Results of such studies suggest that all sperm receptor activity of mZP3 is associated with the C-terminal half of the polypeptide. The essential oligosaccharides are present on just two of five serine residues, serine-332 and -334, in a region of polypeptide near the C-terminus, a region encoded by exon-7 of the *mZP3* gene (8 exons). For example, mutation of either serine-332 or serine-334 to a small aliphatic amino acid results in production of an inactive form of mZP3 in stably transfected cells. Interestingly, of the five serine residues, only these two are conserved from mouse to human ZP3. In this context, the numerous amino acid changes neighboring serine-332 and -334 that have occurred during evolution may impose changes in the structure of O-linked oligosaccharides added to ZP3 and, thereby, affect species specificity of sperm-egg interaction (27, 28). This is currently an active area of investigation in several laboratories.

mZP3 Is an Acrosome Reaction-Inducer

The acrosome is a large secretory vesicle that overlies the nucleus in the apical region of the sperm head (6, 29). The acrosomal membrane just underlying the plasma membrane is referred to as "outer" acrosomal membrane and that overlying the nucleus is referred to as "inner" acrosomal membrane. Morphologically, the AR is seen as multiple fusions between the outer acrosomal membrane and the plasma membrane at the anterior region of sperm head, extensive formation of hybrid membrane vesicles, and exposure of inner acrosomal membrane and acrosomal contents (Fig. 5). Only acrosome-reacted sperm (Fig. 6) can penetrate the ZP and fuse with the egg plasma membrane.

Several of the same kinds of molecules that participate in secretion by somatic cells participate in initiation of the AR (12, 30, 31). These include several signal-transducing components, including G proteins, inositol 3,4,5-triphosphate (IP3) and IP3 receptors, phospholipase C, Ca^{2+}, and voltage-sensitive Ca^{2+} channels. For example, mZP3 stimulation of sperm activates G proteins (G_{i1}, G_{i2}, $G_{q/11}$), depolarizes sperm plasma membrane (from ~ –60 mV to ~ –30 mV), activates Ca^{2+} channels (T-type), and elevates pH (~0.3 units) and intracellular Ca^{2+} concentration (from ~150 nM to ~400 nM). Activation of a pertussis toxin-sensitive G protein complex has been attributed to aggregation of β-galactosyl-

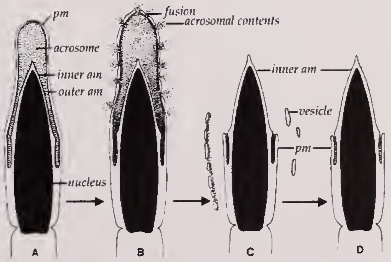

Fig. 5. Diagrammatic representation of the mammalian sperm acrosome reaction. The course of the acrosome reaction is indicated by A-D. An acrosome-intact sperm head is shown in A. In B fusion between outer acrosomal membrane and plasma membrane is indicated. Hybrid membrane vesicles, composed of plasma and outer acrosomal membrane, are shown in C and D. pm = plasma membrane; am = acrosomal membrane.

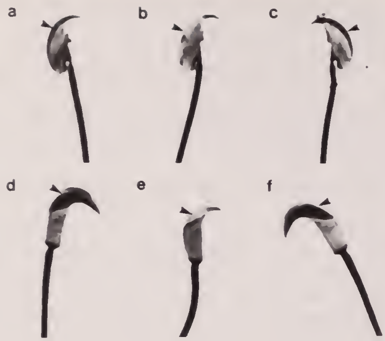

Fig. 6. Acrosome-intact and acrosome-reacted mouse and hamster sperm. Light photomicrographs of mouse (a-c) and hamster (d-f) sperm stained with Coomassie brilliant blue G-250, fixed, and examined by light microscopy. (magnification ~1000X). Acrosome-intact (a, c, d, f) and acrosome-reacted (b, e) sperm are shown. The acrosome reaction was induced with purified egg mZP3 *in vitro*. Arrowheads indicate the position of the acrosome.

transferase on the sperm head, and Ca^{2+} entry through store-operated channels is thought to result from depletion of IP3-sensitive Ca^{2+} stores; both events are triggered by exposure of sperm to mZP3. Finally, in this context, results of recent studies suggest that at least two components essential for intracellular membrane fusion in somatic cells, Rab3A GTPase and SNAREs, are present in mammalian sperm and may participate in membrane fusion during the AR.

It is known that there are many different inducers of the AR (29). However, it is now generally accepted that ZP3 is the natural agonist that initiates the AR upon binding of acrosome-intact mammalian sperm to the ZP (32–34). There are now criteria that distinguish between the so-called "spontaneous" AR and the ZP3-induced AR (e.g., sensitivity to pertussis toxin). While purified mZP3 and large mZP3 glycopeptides induce sperm to acrosome-react *in vitro,* small mZP3 glycopeptides and purified mZP3 O-linked oligosaccharides bind to sperm and inhibit their binding to eggs, but do not induce the AR (5, 14). In the latter context, it has been reported that IgG cross-linking of small mZP3 glycopeptides bound to sperm can induce the sperm to acrosome-react (35). These findings suggest that induction of the AR by ZP3 probably will turn out to be dependent on multivalent interactions between ZP3 and its binding-protein at the sperm surface.

Phenotype of *mZP3* Homozygous Null Mice

The three mouse ZP glycoproteins are organized in a specific fashion in the ZP (6, 36, 37). Each of the glycoproteins is synthesized, secreted, and assembled into a ZP by oocytes during their 2–3-week growth phase (8, 38, 39). The extracellular coat consists of very long filaments composed of mZP2-mZP3 dimers that are cross-linked by mZP1 (Fig. 7). The filaments exhibit a structural periodicity of ~15 nM that represents the positions of mZP2-mZP3 dimers along the filaments. The three glycoproteins are held together in the ZP by non-covalent bonds.

What happens when one of the ZP glycoproteins is not available for assembly of a ZP during oogenesis? The single-copy gene-encoding mZP3 consists of 8 exons (40). *mZP3* null mutant mice ($mZP3^{-/-}$) were produced using homologous recombination in embryonic stem (ES) cells by following standard gene targeting procedures (41, 42). Female $mZP3^{-/-}$ mice were obtained that are indistinguishable in appearance from wild-type littermates and exhibit normal growth. However, $mZP3^{-/-}$ females are infertile and the infertility appears to be related to the complete absence of a ZP surrounding growing oocytes and ovulated eggs (Fig. 8). Examination of superovulated $mZP3^{-/-}$ females revealed that while cumulus masses were always found in their oviducts, frequently no eggs were present within the cumulus

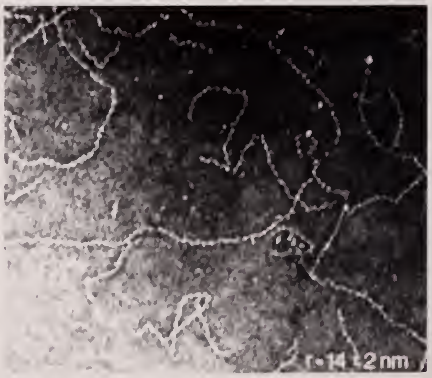

Fig. 7. The ZP is composed of long, cross-linked filaments. Shown is a transmission electron micrograph of mouse egg ZP filaments sprayed onto a grid and negatively stained. The filaments are composed of mZP2 and mZP3 and are cross-linked by mZP1. A structural repeat of 14 ± 2 nanometers along each filament is indicated.

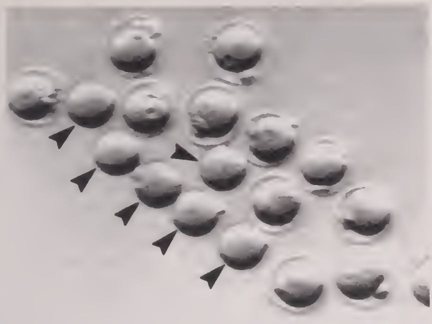

Fig. 8. Ovulated eggs obtained from mice homozygous null for *mZP3* lack a ZP. Shown are six ovulated eggs lacking a ZP recovered from *mZP3*$^{-/-}$ mice (arrowheads) and twelve ovulated eggs which have a ZP recovered from wild-type (*mZP3*$^{+/+}$) mice. The light photomicrograph was taken using Nomarski differential interference contrast microscopy. (magnification ~135X).

masses. In this context, the yield of growing oocytes from ovaries of null mice is a small fraction of that obtained from ovaries of wild-type mice.

These and other observations suggest that in the absence of mZP3, a ZP cannot be assembled around growing oocytes; i.e., mZP3 plays a structural role in assembly and maintenance of the ZP. Furthermore, the absence of a ZP deleteriously affects oocyte growth, follicle development, and fertilization. It seems likely that these effects are attributable to reduced intercellular communication via gap junctions between growing oocytes and innermost follicle cells (*corona radiata*). The viscous border established by the ZP appears to be necessary to stabilize interactions between the two cell types and promote follicle development, including oocyte growth.

Final Comments

There is great diversity when it comes to the mechanism of species-specific fertilization. For example, some non-mammalian eggs lack an extracellular coat (e.g., nematode eggs) while others have a vitelline envelope and a jelly coat (e.g., echinoderm and amphibian eggs). In some species, sperm enter eggs at a particular site (micropyle) without the need for an acrosome reaction (e.g., nematodes), whereas in others sperm undergo the acrosome reaction upon binding to the jelly coat and then bind in a species-specific manner to the vitelline envelope (e.g., echinoderms and amphibians). In the latter context, one might think of the ZP, which is unique to all mammalian eggs, as an amalgamation of the jelly coat and vitelline envelope of some non-mammalian eggs. The ZP is the site of species-specific sperm receptors and an inducer of the acrosome reaction.

I have presented what has been learned about the functions of ZP glycoprotein mZP3 during fertilization, with special emphasis on the role of oligosaccharides in mZP3 function. For example: mZP3 is a structural glycoprotein absolutely required for ZP assembly during oogenesis; mZP3 is a sperm receptor that supports binding of free-swimming sperm to unfertilized eggs; and mZP3 is an acrosome reaction-inducer for sperm bound to the ZP of unfertilized eggs. The sperm receptor and acrosome reaction-inducing activities of mZP3 depend on the glycoprotein's oligosaccharides. In mice, these oligosaccharides apparently are located on two serine residues located near the C-terminus of the polypeptide. This portion of the polypeptide has undergone significant changes during evolution, and it is possible that these changes result in alternative oligosaccharide structures for ZP3 from different mammalian species. The cell's rules for O-linked glycosylation of nascent proteins will have to be determined in order to answer key questions about ZP3 oligosaccharides.

Although we know a great deal about mZP3, many more questions remain. A pressing issue concerns the nature of the protein associated with plasma membrane surrounding the sperm head that recognizes and binds to mZP3 oligosaccharides (so-called, egg-binding protein). This area of research, while extremely productive, remains inconclusive (6). A second issue concerns the nature of the ZP3 oligosaccharides that are recognized by sperm. We know very little about the structure of these oligosaccharides (e.g., composition, sequence, and linkages) or their sites on ZP3 polypeptides from different species of mammalian eggs. Can these oligosaccharides account for the species-specific binding of sperm that is observed experimentally? Finally, the mechanism by which inactivation of mZP3 inactivates the sperm receptor following fertilization needs to be worked out. Preliminary evidence suggests that inactivation can be attributed to enzymatic destruction of essential mZP3 oligosaccharides (PM Wassarman, unpublished results). We hope that answers to these and other questions will be forthcoming and that such progress will be of some benefit to clinicians involved in the manipulation of human reproduction.

Acknowledgments

For more than twenty years many outstanding research assistants, graduate students, and postdoctoral fellows, at Harvard Medical School, the Roche Institute of Molecular Biology, and Mount Sinai Medical School, have contributed to the research described here. I am grateful to all of them for their scientific contributions and for the spirit they imparted to our laboratory. This research is currently supported by the NICHD (HD-35105).

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Mechanisms of Type I Interferon Cell Signaling and STAT-Mediated Transcriptional Responses

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Abstract

The interferons are pleiotropic cytokines that are induced in response to virus infection and act in a paracrine fashion to elicit an antiviral state in nearby cells. Binding of interferons to their cell surface receptors induces a tyrosine kinase signaling cascade that leads to the activation of latent cytoplasmic signal-transducer-and-activator-of-transcription (STAT) factors. Activated STATs then translocate into the nucleus and are targeted to conserved promoter-enhancer sites to induce the transcription of interferon-responsive genes that encode for proteins with potent antiviral, growth-inhibitory, antitumor, and immunomodulatory properties. Although the signaling and activation phase of the interferon response has been well characterized, several recent findings have further clarified the cellular events that immediately follow STAT activation, including the identification of the amino acid signals that regulate the subcellular distribution of interferon-signaling proteins. To achieve their full transcriptional capacity, members of the STAT family of transcription factors have been shown to require interactions with an assortment of nuclear transcriptional co-activator proteins. A number of the STAT co-activator protein partners have only been identified recently. Some of these interactions suggest cross-talk with other signaling pathways, thereby reaffirming the far-reaching, yet undiscovered, properties of interferons.

Key Words: Interferon, transcription, co-activators, chromatin, STAT1, STAT2, p48, IRF9, nuclear localization signals (NLS), nuclear export sequences (NES).

Glossary

ATP: adenosine triphosphate
BRCA: breast cancer susceptibility marker
cAMP: cyclic adenosine monophosphate
CBP: CREB-binding protein
CREB: cAMP-response-element-binding protein
Crm1: chromosome region maintenance 1
DNA: deoxyribonucleic acid
GAF: gamma-activated factor
GAS: gamma-interferon-activated sites
GFP: green fluorescent protein
GTF: general transcription factor
HAT: histone acetyltransferase
HDAC: histone deacetylase
IFN: interferon
IFNAR: IFNα/β receptor
IL-2: interleukin-2
IRF: interferon regulatory factor
ISG: interferon-stimulated gene
ISGF3: interferon-stimulated gene factor 3
ISRE: interferon-stimulated response element
JAK: Janus kinase
MCM: minichromosome maintenance
MHC: major histocompatibility complex
NES: nuclear export sequences
NLS: nuclear localization signal
NMi: N-Myc interactor
PIAS1: protein inhibitor of activated STAT1
PMSP: proline-methionine-serine-proline
PRMT1: protein arginine methyl-transferase
PSP: proline-serine-proline
RNA: ribonucleic acid
SH2: src homology 2
STAT: signal transducer and activator of transcription
TAD: transcriptional activation domain
TAF: TBP-associated factor
TBP: TATA-binding protein

Introduction

MOST CELLS POSSESS THE INNATE ABILITY to fight viruses. Virus infection directly activates the transcription of Type I interferon (IFNα/β) genes in infected cells. The secreted Type I IFN cytokines bind to their cell surface receptors on adjacent cells to activate the formation of the interferon-stimulated gene factor 3 (ISGF3) transcription factor complex, the primary regulator of antiviral gene transcription by IFNα. ISGF3 is composed of two signal-transducer-

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and-activator-of-transcription (STAT) proteins, STAT1 and STAT2, and the interferon regulatory factor (IRF) protein IRF9 (also known as p48 or ISGF3γ) (Fig. 1). The activated trimeric complex then becomes competent for translocation from the cytoplasm to the nucleus, to initiate the transcription of interferon-stimulated genes (ISGs) that encode for proteins with potent antiviral, antiproliferative, antitumor, and anti-inflammatory effects (1).

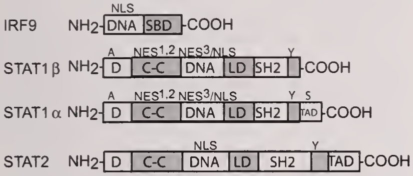

Fig. 1. Proteins of the ISGF3 complex. STAT1, STAT2 and IRF9 combine to form the Type I IFN-activated ISGF3 complex that mediates interferon-stimulated response element (ISRE)-dependent antiviral gene transcription. IRF9 is a 393-amino acid protein with an N-terminal DNA-binding domain (DNA) and a C-terminal STAT-binding domain (SBD). STAT1β is an alternatively-spliced isoform of the 750-amino acid STAT1α, which has the additional C-terminal 38-amino acid transcriptional activation domain (TAD). STAT1 is phosphorylated on Tyr701 (Y) and Ser727 (S). The 851-amino acid STAT2 is phosphorylated on Tyr689 (Y), but lacks a phosphoserine site in its TAD. The nuclear localization signals (NLS) are located within the protein domains as indicated. The three STAT1 nuclear export signals (NES^{1-3}) are located in the domains as shown. Post-translational modification sites: A=STAT1 PRMT1 arginine 31 methylation site; Y=tyrosine 701 phosphorylation site; and S=serine 727 phosphorylation site. D=domain responsible for dimer-dimer interactions, C-C=coiled-coil domain, DNA=DNA-binding domain, LD=linker domain, SH2=src-homology 2 domain, and TAD=transcriptional activation domain.

Activated T lymphocytes and natural killer cells also help regulate antiviral responses in the adaptive immune response by producing the Type II interferon (IFNγ) cytokines. IFNγ, which is distinct from but functionally related to Type I IFNs, binds to a different cell surface receptor, leading to the activation and formation of a homodimeric STAT1 complex, called the gamma-activated factor (GAF) complex. In addition to antiviral responses, IFNγ is also a key regulator of cell proliferation and is involved in tumor surveillance (2).

Although the activation of the ISGF3 and GAF transcription factor complexes has been well studied in the last decade, since the discovery of STATs, comparatively little is known about how activated STAT proteins enter the nucleus, communicate with the ribonucleic acid (RNA) polymerase holoenzyme complexes to initiate gene transcription, and re-enter the cytoplasm once the transient transcriptional response to IFN has subsided. It has become apparent that components of the ISGF3 and GAF complexes are actively shuttled between the cellular compartments. Macromolecular transport across the nuclear pore complex in both directions is an energy-requiring, tightly regulated event for cargo proteins exceeding ~40-kDa (3, 4). A family of soluble shuttling transport receptors called importins or karyopherins mediates the nuclear import of proteins. During the nuclear import process, one of several proteins from the importin-α family recognizes and binds to its specific amino acid sequences called nuclear localization signals (NLS) on the cargo protein. Transport of proteins in the opposite direction, from the nucleus to the cytoplasm, is regulated by the family of exportin proteins that recognize characteristic leucine-rich nuclear export sequences (NES) on cargo proteins destined to leave the nucleus (5 – 8). Recent advances from several laboratories, including ours, have demonstrated that the subcellular distribution of ISGF3 protein components is regulated by novel NLSs and NESs (9 – 13).

Ample recent evidence (14) also demonstrates that the STATs, like many transcription factors, initiate gene transcription with the help of transcriptional co-activators. Transcriptional co-activators describe a broad range of nuclear proteins that are important in bringing about the full gene expression capacity of transcription factors. Co-activators have diverse functions, and those that have already been well characterized assist primarily in the delivery of activating signals to the basal transcription machinery that is present in most active genes, and/or in the remodeling of chromatin structure to allow transcription factor access to the promoter. The precise roles that the various STAT-co-activator protein interactions play in Type I and Type II interferon antiviral signaling pathways, and thus, in antiviral gene transcription, are still unclear and are the focus of intense research. This review will focus on the latest findings in IFN signaling following receptor activation, and examine several STAT-co-activator protein interactions and their potential importance in Type I (ISGF3-mediated) and Type II (GAF-mediated) IFN-dependent gene expression.

The Type I IFN Signaling Pathway

The Type I interferons are a gene family consisting of a single IFNβ gene and at least twelve immediate-early and delayed-early IFNα genes that function in most cells by activating interferon-responsive gene expression (15–18). IFNα/β also regulates adaptive antiviral immune responses involving dendritic and natural killer cells (19). Unlike other STAT-signaling pathways, the Type I IFN pathway involves two protein families, the STATs and IRFs, which work together to form the ISGF3 complex that activates ISG expression (Fig. 2). Proteins encoded by ISGs have antiviral properties, and elicit their effects by interfering with cellular or viral processes such that viral replication becomes blocked or impaired (1). The direct inhibition of the viral replicative life cycle, arrest of cell cycle progression, and increasing of cellular susceptibility to apoptosis are common mechanisms by which antiviral proteins limit the extent of viral spread (20, 21). While a number of ISGs and IFN-induced antiviral proteins have been well defined (17), the biological functions for many remain unclear. A recent oligonucleotide microarray analysis has identified at least 300 ISGs induced by both IFNα and IFNβ, many of which were previously unknown (22).

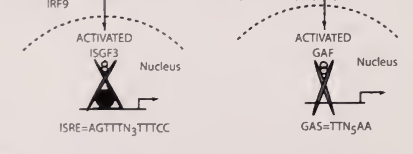

Fig. 2. The Type I and Type II IFN pathways. IFNα/β and IFNγ, which are functionally related but structurally distinct cytokines, bind to different cell surface receptors. IFNα/β activates the Type I IFN pathway, leading to the oligomerization of STAT1, STAT2, and IRF9 to form ISGF3. IFNγ activates the Type II IFN pathway, which directs the homodimerization of two STAT1 molecules to form GAF. Both activated ISGF3 and GAF complexes translocate into the nucleus where they bind to promoters with ISRE and GAS sequences, respectively.

Once the activated ISGF3 complex has entered the nucleus, the IRF9 component acts as a sequence-specific deoxyribonucleic acid (DNA)-binding protein and confers recognition upon the activated STAT1:2 heterodimer (23–26). The contribution of IRF9 as an adapter for the STAT1:2 heterodimer represents a unique feature of the ISGF3 complex, as other STAT-signaling pathways involve STAT homodimers that bind directly to DNA. The ISGF3 complex binds to and activates transcription of genes through the conserved interferon-stimulated response elements (ISRE; AGTTTN3TTTCC) (27).

STAT1 and STAT2 represent two of seven mammalian STAT family members that range in size from 90–115-kDa (28). Protein sequence alignment and crystallographic analyses of STAT1, STAT3, and STAT4 reveal that the STAT transcription factors collectively feature high amino acid homology over several distinct protein regions having defined structural and functional roles (29–31). From studies of the STAT4 crystal structure, the amino-terminal domain (residues 1–123) was found to stabilize reciprocal interactions between two STAT dimer complexes bound to tandemly arranged promoter sites (31). The DNA-binding cores of STAT1 and STAT3 have been crystallized and observations reveal several distinct structural domains: an α-helical coiled-coil region (residues 136–317 of STAT1), a highly-conserved DNA-binding domain which possesses an immunoglobulin-type fold (residues 318–488), a conserved src-homology 2 (SH2) domain (residues 577–683) that interacts with phosphorylated tyrosine motifs, and an α-helical linker domain (residues 488–576) that bridges the DNA-binding and SH2 domains (29). The carboxyl-terminal end of STATs was too unstable to resolve for crystallographic analyses, but the region has been determined to be the important transcription activation domain (TAD), a region that interacts with additional proteins (14). It is the NH_2-terminal coiled-coil domains of STAT1 and STAT2 that interact with IRF9 to form ISGF3 (19). The 48-kDa IRF9 protein possesses a conserved amino-terminal DNA-binding domain and a carboxyl-terminal STAT-binding domain (Fig. 1). With the exception of a nuclear localization signal in the DNA-binding domain (described below), additional functional domains within the IRF9 protein have not yet been described.

The Type II IFN Signaling Pathway

The Type II interferon, IFNγ, is encoded by a single gene, and plays an essential role in the regulation of the adaptive immune response. Binding of IFNγ to its receptor leads to the homodimerization of STAT1 proteins via intermolecular SH2-phosphotyrosine interactions to form GAF (Fig. 2) (32). The GAF complex then translocates into the nucleus to bind to conserved gamma-interferon activated sites (GAS; TTN_5AA) on the promoters of IFNγ-responsive genes. Unlike the ISGF3 complex, which uses the IRF9 protein as its DNA-binding adapter, the GAF complex binds to DNA directly. Many target genes induced by the IFNγ-activated GAF complex have been identified; further information can be found in references (2, 33).

STAT1 and STAT2 Are Essential for Innate Immunity

Mice deficient in STAT1 and STAT2 have been generated by gene targeting, and the observed phenotypes for both strains have revealed their important roles in the regulation of immune responses (34–36). STAT1 knockout mice are viable and undergo normal development. Based on studies from cell lines, a loss of STAT1 should affect both Type I and II IFN functions. Indeed, IFN-dependent responses were found to be absent, which increased their susceptibility to viral infections and certain microbial pathogens (34, 35). Numerous studies have also demonstrated the growth inhibitory properties of IFNs, suggesting that these cytokines play a role in controlling tumor growth. In support of this hypothesis, STAT1-deficient mice had a higher incidence of both spontaneous and methylcholanthrene-induced tumors than normal controls, suggesting a role for STAT1 as a tumor suppressor (37). Tumors also formed at an even higher rate in mice that were bred into a p53-null background. Together, these observations suggested the involvement of IFNγ in tumor surveillance. It is believed that a loss of STAT1 eliminates the ability for IFNγ to promote STAT1-dependent antigen processing and presentation by major histocompatibility complex (MHC) class I and II molecules, therefore allowing cancer cells to grow unchecked.

Like their STAT1 knockout mice counterparts, the STAT2-deficient mice are also viable and undergo normal development. As anticipated, STAT2 knockout mice were highly susceptible to viral infections due to defective IFN signaling (36). However, more subtle changes in fibroblasts derived from STAT2-deficient mice were identified. One interesting observation was that the levels of the STAT1 protein were lower in $STAT2^{-/-}$ fibroblasts than in wild-type cells. This finding suggests that there may be a STAT2-dependent autocrine loop that maintains basal Type I IFN production and activity, which in turn sustains the steady-state expression of the interferon-responsive STAT1 gene. The loss of STAT2 therefore affected both Type I and Type II IFN-dependent transcriptional responses. The study also shows that macrophages, dendritic cells, and stromal fibroblasts derived from $STAT2^{-/-}$ animals can no longer perpetuate more Type I interferons to support the autocrine/paracrine loops, thus altering their ability to regulate lymphocyte maturation and function (36). Future studies may reveal additional immunologic defects in STAT2-deficient mice.

ISGF3 Complex Assembly

While the mechanisms of Janus kinase-STAT (JAK-STAT) activation at the IFNα/β receptor have been extensively studied, more recent work described in this section has begun to reveal the dynamics of trimeric ISGF3 complex assembly following IFN stimulation. Also, several reports have shed light on the mechanisms and amino acid signals that govern the subcellular distribution of the ISGF3 signaling components (9–13).

Binding of IFNα/β to its cell surface receptor leads to the rapid receptor-dependent activation of latent cytoplasmic STAT1 and STAT2. Together with IRF9, they form the trimeric ISGF3 protein complex (38–40). Two subunit chains form the IFNα/β receptor (IFNAR), the α chain or IFNAR1, and the β chain or IFNAR2, which is composed of the β_{short} (β_S) and β_{long} (β_L) transmembrane forms (Fig. 3) (41). Ligand binding induces dimeric aggregation of receptor chains, and activates receptor-associated Janus kinases JAK1 and TYK2. TYK2 then phosphorylates a specific tyrosine residue at position 466 on the cytoplasmic receptor tail of IFNAR1 (42). This phosphotyrosine serves as a docking site for the rapid recruitment of latent cytoplasmic STAT2 via its SH2 domain (43). Association of STAT2 with the cytoplasmic tail of the IFNAR β_L chain has

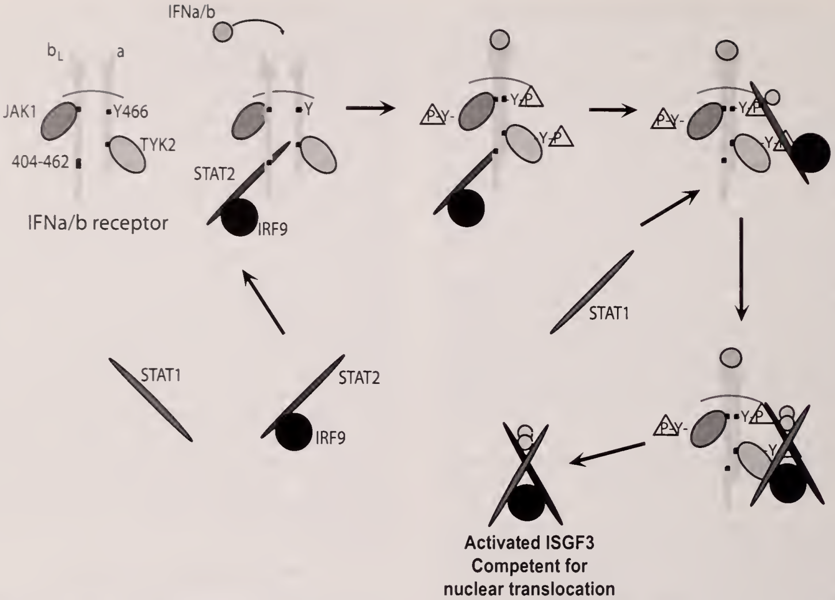

Fig. 3. The IFNα/β receptor and ISGF3 complex assembly. The IFNα/β receptor (IFNAR) is composed of two subunits—the IFNAR1 (α) and the IFNAR2 (β_L or β_S) chains. Constitutive and IFN activation-dependent STAT2-binding sites have been mapped at the cytoplasmic tail of IFNAR, as indicated. Binding of IFNα/β dimerizes the receptor and activates receptor-associated Janus kinases (JAKs) JAK1 and TYK2. TYK2 then phosphorylates tyrosine 466 on the ? chain, which recruits STAT2 via its SH2 domain. Tyrosine 690 on STAT2 then becomes phosphorylated, which allows for the docking of the STAT1 protein. STAT1 also becomes phosphorylated at tyrosine 701, allowing for the heterodimerization of STAT1 and STAT2. The STAT1:STAT2 heterodimer is now competent for nuclear translocation. The IRF9 protein is associated with STAT2 in the cytoplasm and may play a role in ISGF3 complex assembly at IFNAR.

been reported to occur in both the absence (44) and presence (43) of Type I IFN signaling. Interestingly, the mapped regions for interaction with STAT2 within the IFNAR β_L cytoplasmic tail differ between the activated and inactivated states (45).

Once anchored to the receptor tail, STAT2 is then phosphorylated by TYK2 on tyrosine 690, which serves to recruit cytoplasmic STAT1 (46, 47). STAT1 is then subsequently phosphorylated on tyrosine 701, allowing for the heterodimerization of STAT1 and STAT2 (48). The activated STAT1:2 heterodimer forms while bound to the intracellular domain of the IFN receptor, and upon release, the complex becomes competent for nuclear import. It has generally been assumed that the STAT1:STAT2 heterodimer joins with their obligatory partner, IRF9, to form ISGF3 at some point during the course of translocation into the nucleus, but the subcellular compartment where this event takes place was only recently defined. The IRF9 protein apparently plays an active role in ISGF3 complex assembly in the cytoplasm. Although the IRF9 protein was found to be a constitutively nuclear protein when expressed in cells (see below), the co-expression of the STAT2 protein retains IRF9 protein in the cytoplasm via direct protein interactions, indicating that the two proteins form cytoplasmic complexes even in the inactivated state (9). Interestingly, the cytoplasmic tail of the IFNα/β receptor β_L chain can recruit IRF9 only in the presence of STAT2 (Lau JF and Horvath CM, unpublished observations).

These observations suggest that the STAT2:IRF9 protein complexes could be involved with ISGF3 complex oligomerization at or near the receptor in the cytoplasmic compartment. The presence of STAT2:IRF9 cytoplasmic complexes at the IFN receptor may also provide a ready protein pool for rapid ISGF3 complex assembly, which is characteristic of the fast activation kinetics observed in the interferon response.

ISGF3 Subcellular Distribution

The subcellular distribution of STAT proteins is regulated in response to extracellular stimuli. While localized within the cytoplasm during the inactivated state, STAT complexes can be found within the nucleus after several minutes of IFN treatment (23). In the Type II IFN pathway, STAT1 proteins are recycled and returned to the cytoplasm within hours of their inactivation by a yet-to-be-identified nuclear phosphatase (49, 50). Further, the STAT2 protein exhibits a similar activation-inactivation cycle following IFNα treatment, suggesting that the recycling of STAT2 to the cytoplasm is an essential component of Type I IFN signaling (Radulescu VC and Horvath CM, unpublished observations). The STAT proteins also move about within the cell in a haphazard, "random-walk" fashion, even after activation by the JAK-receptor complex (51). Although shown to be important for certain transcriptional regulators such as the SMAD (similar to mothers against decapentaplegic) proteins of the TGFβ signaling pathway, the translocation of activated STAT1 dimers from the cytoplasmic face of the cell membrane into the nucleus does not rely on movement along actin cytoskeletal or microtubular networks (51, 52).

Early efforts to determine the amino acid sequences that govern STAT transport through the nuclear pore were hampered by the lack of classical NLS or SV40-like NES motifs. An initial study demonstrated the importance of the highly conserved amino-terminal domain (residues ~1 – 134) in regulating the nuclear accumulation of STAT1 (53). Also, STAT1 has been demonstrated to interact with the importin/karyopherin protein NPI-1, therefore implying that STATs utilize importin/karyopherin proteins to gain access into the nucleus (54). Recently, several laboratories determined the chemical structures of the STAT NLS and NES. Determination of the surface structure of the STAT1 and STAT2 nuclear localization signals (NLSs) was facilitated by the three-dimensional crystal structure of STAT1 which identified an arginine/lysine-rich region in the DNA-binding domains of both STAT1 and STAT2 (10). Because an NLS is often characterized by the presence of basic amino acids (55), a surface region bearing high concentrations of arginine and lysine served as an attractive focus to identify NLS candidates. Mutation to these basic amino acids abrogated the ability of the modified STAT1 and STAT2 proteins to enter the nucleus, and therefore implicated the arginine/lysine-rich region in mediating contact with proteins involved in the nuclear import process. Further, while the STAT NLS was being determined, three different groups reported the identification of three different NESs within the STAT1 protein that regulated its nuclear export (11 – 13). Mutation to each NES site eliminated the ability for these modified STAT1 molecules to exit the nucleus in an exportin 1/chromosome region maintenance 1 (Crm1)-dependent process. Two NES sites lie within the coiled-coil region (12, 13), while the third resides within the adjacent DNA-binding domain (11). These sites may be situated closely to each other in the natively folded protein and therefore represent multiple contact points for the exportin machinery. It is still unclear whether the nuclear export of STAT2 and other STAT proteins is regulated similarly to STAT1, but these amino acids are conserved.

The remaining component of the ISGF3 complex, the IRF9 protein, was initially found in both the nucleus and the cytoplasm, regardless of IFN stimulation (23, 56). Since the apparent molecular weight of the IRF9 protein approaches the theoretical diffusion limit for the nuclear pore complex (which is approximately 50-kDa), IRF9 was hypothesized to diffuse freely between the cytoplasm and nucleus. The finding that a green fluorescent protein (GFP)-IRF9 fusion protein, that was well beyond the theoretical diffusion limit for the nuclear pore complex, is constitutively targeted to and accumulates within the nucleus when expressed in cells detracts from the diffusion theory. Using fragments of IRF9 fused to GFP, the nuclear import signals were mapped to two interdependent clusters of arginines and lysines located in its DNA-binding domain (9). The two basic amino acid clusters, spaced apart by ten amino acids, is in agreement with a variation of the bipartite NLS motif (57). The novel IRF9-bipartite NLS motif is also conserved in two closely related IRF proteins, IRF4 and ICSBP/IRF8, signifying the generality of this novel NLS in a subset of IRF proteins.

Thus, these findings suggest there may be two pools of IRF9—one that is constitutively nuclear by virtue of its bipartite NLS, and a second that is complexed with STAT2 in the cytoplasm. The IRF9 protein, once regarded as an inert DNA-binding adapter for STATs, now appears to play an active role in regulation of ISGF3-cell-signaling events. One can envision that upon receptor activation by IFNα/β, STAT2 may bring along IRF9 to the receptor for oligomerization with STAT1. Alternatively, an activated STAT1:STAT2 heterodimer may translocate into the nucleus to join IRF9 at the ISRE-containing promoter. Because IRF9 is actively transported into the nucleus, it will be important to determine whether the protein possesses transcriptional functions independent of STAT1 and STAT2.

ISGF3-Independent Functions of IRF9

Several reports suggest that the IRF9 protein indirectly modulates the activities of several diverse genes, including the IP-10 chemokine gene that is involved in inflammatory and neoplastic responses (58), and the enhancer-1 region responsible for regulating gene expression in the hepatitis B virus (59, 60). In a more recent study, the overexpression of IRF9 in a specific breast cancer cell line led to its resistance to treatment with antimicrotubule agents such as paclitaxel (61). Overexpression of STAT1 or STAT2, or treatment with IFNα, did not produce the same drug-resistance phenotype, making this event independent of ISGF3 functions and IFNα activation. Although the overexpression of IRF9 led to the expression of several interferon-responsive genes, it remains unclear whether IRF9 or any of the induced ISG proteins play a direct role in conferring drug resistance. Importantly, the study also identified that IRF9 was highly expressed in a number of breast and uterine tumor samples, suggesting that high IRF9 protein levels may serve as potential markers for drug resistance in specific tumor types.

Transcriptional Activation and ISGF3

While the ISGF3-independent transcriptional functions of the IRF9 protein are not entirely understood, the roles played by STAT proteins are better defined. The STAT proteins have carboxyl-terminal transcriptional activation domains that contribute to gene transcription. Because either the transcriptionally active STAT1α (the 91-kDa full-length protein), or its splice variant STAT1β (lacking the C-terminal 38 amino acid TAD), can be used interchangeably for Type I IFN signaling, it has been generally accepted that ISGF3-mediated transcriptional signals derive from the STAT2 protein (Fig. 1) (46, 62). It has also been demonstrated previously that at least the C-terminal 40 residues from STAT2 are required for full ISG transcription (47). A protein fragment of at least 116 residues from the STAT2 carboxyl-terminal TAD was also shown in heterologous DNA-binding domain fusion experiments to contain the necessary determinants to make this domain a potent transcriptional activator in isolation (47, 63–66). Interestingly, there is little amino acid sequence homology between the human and murine STAT2 proteins at their carboxyl-termini, but both domains have been shown to interact with a distinct but overlapping set of cellular proteins, including the histone acetyltransferase cAMP-response-element-binding protein (CREB)-binding protein (CBP)/p300 (63, 64). Thus, despite divergent amino acid sequences between species, the functions of the STAT2 C-terminal TADs appear to be conserved.

The mechanisms by which the STAT2 TAD elicits ISG transcription remain obscure. However, the TADs of other STAT proteins employ a number of mechanisms to regulate transcription. One level of regulation is achieved through a cytokine-induced phosphorylation event that takes place within the STAT TAD. Several STAT proteins possess in their TADs a key serine residue within a conserved proline-methionine-serine-proline (PMSP, in STATs 1, 3, and 4) or proline-serine-proline (PSP, in STATs 5a and 5b) motif that becomes phosphorylated in response to cytokine treatment (67). Serine phosphorylation in both STAT1α and STAT3 is required for maximal transcriptional activities. When STAT1α lacks this serine residue (serine 727), only 20% of the wild-type transcriptional capacity is retained, producing defects in IFN responses (68). The STAT2 TAD does not possess the PMSP/PSP motif, and is therefore not regulated by serine phosphorylation. However, because the carboxyl-terminus of STAT2 TAD is indispensable for Type I IFN responses, it will be interesting to determine whether this region is post-translationally regulated in some other fashion.

Although it is becoming well documented that the carboxyl-terminal STAT TADs, and in particular, those of STAT1 and STAT2, are potent and specific co-activator recruiters, it is worthy to note that other STAT structural domains have been implicated in transcriptional regulation. For instance, a novel functional interaction was found in a yeast two-hybrid screen between the coiled-coil domains of all STAT proteins (with the exception of STAT2) with a protein called Nmi (N-Myc interactor) (69). The Nmi protein enhanced STAT1-dependent transcriptional responses to both IFNγ and interleukin-2 (IL-2). In a separate study, a key pair of lysine and glutamic acid residues within the STAT1 linker domain was found to be important for Type I IFN GAS-dependent transcriptional activities (70), but the mechanism for this defect is unknown.

Much of the earlier work on STAT-protein post-translational regulation has focused on tyrosine and serine phosphorylation events. More recently, the activity of the STAT1 protein has been shown to be regulated by methylation as well. The protein arginine methyl-transferase (PRMT1) was found to associate with STAT1, which allowed for the methylation of a highly conserved arginine residue (arginine 31) located at the STAT1 amino-terminus (71). Interestingly, PRMT1 was previously reported to associate with the cytoplasmic tail of the IFNα/β receptor in a yeast two-hybrid assay, and the elimination of PRMT1 activity by antisense oligonucleotides reduced Type I IFNs antiviral signaling capabilities (72). The use of a specific inhibitor to eliminate PRMT1 activity also impaired Type I IFN-dependent transcriptional responses, suggesting the importance of methylation in transcriptional responses involving STAT1. Thus, the post-translational modification of STAT1 appears to be as important as the integrity of the STAT2 carboxyl-terminus TAD in Type I IFN signaling. The methylation of STAT1 is thought to enhance its ability to bind DNA, and prevents its interaction with the protein inhibitor of activated STAT1 (PIAS1) protein, a known inhibitor of STAT1-dependent transcription.

Overview of Transcriptional Activation

Gene transcription has been shown to be a dynamic process involving numerous protein factors and DNA-chromatin structural changes. It is plausible to consider that a series of nuclear catalytic events need to take place both before and after the ISGF3 complex gains access to the ISG-promoter region. General models of inducible gene expression for a variety of other transcriptional regulators have shown that tightly wrapped chromatin is usually inhibitory for gene expression, likely due to physical obstruction of promoter-binding sites that prevent access to transcription factors, co-activators, and RNA polymerase holoenzyme subunits. In the transcriptionally inactive state, the DNA template is intimately associated with core histone subunits, which collectively make up what is called a nucleosome. To gain access to the DNA template and its promoter-enhancer elements, transcription factors may recruit one or several nuclear co-activators that regulate transcriptional activity by covalent modifications of core histones (i.e., by acetylation, phosphorylation, and methylation), or by structural changes that alter the DNA-histone association (73–75).

One class of chromatin-modifying co-activators is the histone acetyltransferases (HATs), which has been shown to potentiate the activity of several groups of transcription factors (76–81). Protein complexes with HAT activities have been tightly linked with the remodeling of chromatin by acetylation of highly conserved lysine residues on the amino-terminal tails of core histones (82, 83). The transfer of negatively-charged acetyl groups onto specific lysine residues on the positively-charged histone molecules is thought to create a repulsive force between the negative charges of the hyperacetylated histones and the chromatin template, allowing for the more relaxed chromatin-DNA conformation. The family of HAT co-activators includes the CBP/p300, GCN5, P/CAF, and p160 proteins (84). The family of histone deacetylase (HDAC) proteins catalyzes the reverse reaction, which is generally repressive for gene expression. More specific reviews of the roles of HDACs in gene transcription can be found in articles by Gray and Ekstrom (85) and by Ng and Bird (86).

Not all histone-modifying proteins are acetyltransferases. Chromatin regulation also depends on other types of histone tail modifications such as lysine and arginine methylation and tyrosine phosphorylation (87, 88). The STAT1 methyltransferase PRMT1 also modifies histones by methylation on conserved arginine residues. Another class of co-activator proteins remodel chromatin structure in adenosine triphosphate (ATP)-dependent fashion, and includes SWI/SNF and RSC proteins (75, 89, 90). These ATPases are thought to generate super-helical torsion of the DNA template, forcing the DNA apart from histones (90, 91).

Emerging evidence demonstrates that the various chromatin-modifying proteins work together in well-orchestrated fashion to activate antiviral gene expression. The systematic recruitment of several HAT proteins—first GCN5, then CBP (in association with RNA polymerase II), and finally, the SWI/SNF complex—was shown to be required for the remodeling of the nucleosome structure of the IFNβ gene locus (92, 93).

A number of transcriptional regulators also directly or indirectly recruit co-activator proteins that primarily serve as architectural links between promoter-bound gene-specific and general transcription factors (GTFs). These proteins include integral components of the basal transcription core machinery, such as GTFs (such as TFIIA, B, D, E, F and H), the TATA-binding protein (TBP), and TBP-associated factors (TAFs). Another co-activator family is represented by the multi-protein metazoan Mediator complex. First genetically identified in yeast, the Mediator is an essential part of the RNA polymerase II holoenzyme complex that is responsible for transcription. Mediator homologues were soon found in humans and now include several multi-protein complexes, such as the thyroid hormone receptor associated protein (TRAP), vitamin D_3 receptor interacting protein(s) (DRIP), and activator-recruited cofactor (ARC) complexes (75, 94, 95). Functional interactions with the mediator complex components are mostly limited to transcriptional regulators that belong to the lipophilic nuclear receptor superfamily (such as the vitamin D and thyroid hormone receptors), and to a handful of non-nuclear receptor transcriptional regulators such as p53 and Sp-1 (75, 94–96).

Recruitment of Transcriptional Co-activators by STATs

Transcriptional regulation by STAT proteins is in large part achieved by the recruitment of general or gene-specific transcriptional co-activators by their carboxyl-terminal transcriptional activation domains (summarized in the Table). One protein that has been reported to interact with several STAT proteins at their C-terminal TADs is CBP/p300. STATs 1, 2, 5, and 6 have been shown to recruit CBP/p300 (65, 97–100). Interestingly, the STAT1 protein also interacts with CBP/p300 at its N-terminal end (97). STATs likely recruit CBP/p300 to remodel chromatin structure at target gene loci to enhance promoter accessibility for the activated STAT complexes, and possibly for additional regulators that contribute to transcriptional synergy. With respect to Types I and II IFN signaling pathways, the recruitment of the CBP/p300 protein enhances ISRE- and GAS-dependent transcriptional responses (65, 97), suggesting the importance of HAT activities in IFN responses. While the STAT2 carboxyl-terminal TAD is critically important for Type I IFN responses, it is unclear whether the STAT2-CBP/p300 interaction is the one that makes this domain indispensable. Further, while it is recognized that histones are targets for acetylation by the CBP/p300 proteins, the STATs themselves have recently been shown to be substrates as well. One recent study showed that CBP acetylation of STAT6, in addition to histones, was required for the transcription of the 15-lipoxygenase-1 (15-LOX-1) gene (101).

TABLE

Proteins That Interact with ISGF3 Components

ISGF3 Component	Interacting Partners	Comments
IRF9	STAT1, STAT2	The carboxyl-terminal STAT-binding domain (SBD, see Fig. 1) mediates contact with the coiled-coil regions of STAT1 and STAT2.
STAT1	CBP/p300, MCM5, BRCA1, Sp1, Nmi-1, TFII-I	The histone acetyltransferase CBP/p300 contacts STAT1 at both the amino-terminus and the carboxyl-terminal transcriptional activation domain (TAD). Both MCM5 and BRCA1 are recruited following serine-727 phosphorylation in the Type II IFNγ-dependent signaling pathway. The involvement of STAT1 co-activators in Type I IFN ISGF3-dependent signaling remains unclear.
STAT2	CBP/p300, IRF9, STAT1	CBP/p300 interacts with the carboxyl-terminal STAT2 TAD.

Thus, in addition to post-translational amino acid modifications by tyrosine/serine phosphorylation and arginine methylation, the functions of STATs are also regulated by acetylation. Also, it will be interesting to determine whether STAT1 or STAT2 is a target for acetylation, much like STAT6, under certain physiologic conditions.

For several STAT proteins bearing the PMSP/PSP phosphoserine module, phosphorylation of this highly conserved carboxyl-terminal serine is a prerequisite for the recruitment of co-activator proteins that aid STATs in enhancing gene transcription (67). For STAT1α, cytokine-induced serine 727 phosphorylation leads to the direct recruitment of transcriptional co-activators. One interacting co-activator is MCM5, a member of the highly abundant minichromosome maintenance (MCM) protein family. Co-expression of STAT1α with MCM5 enhanced GAS-dependent reporter gene activity (102). STAT1-associated MCM5 in turn binds MCM3, suggesting the recruitment of a multimeric protein complex to the STAT1 TAD (103). MCM proteins, which possess DNA helicase activities thought to catalytically unwind DNA, are required for DNA replication control and are often found associated with other proteins such as the origin-replication complex at the initiation site of DNA replication. MCM proteins also interact with the RNA polymerase II holoenzyme (104), which may link helicase DNA-unwinding functions with transcriptional control in IFN-dependent gene expression. The specific nature of MCM-STAT interactions is still being investigated.

Another protein found to be recruited by the STAT1 TAD is the breast and ovarian cancer susceptibility marker BRCA1. The role of BRCA1 in DNA repair is well described, but there is emerging evidence that supports its role as a transcriptional regulator (105, 106). It has been found that BRCA1 works in conjunction with STAT1 to differentially induce an IFNγ-responsive gene involved in growth inhibition (107). BRCA1 and STAT1 were found to synergistically induce the expression of cyclin-dependent kinase inhibitor *p21WAF1* in response to IFNγ stimulation. STAT1 could not activate *p21WAF1* transcription in BRCA1-deficient breast cancer cells. Importantly, the recruitment of BRCA1 by STAT1α was shown to be dependent on serine 727 phosphorylation (107). The role of BRCA1 as a co-activator for other STAT1 transcriptional activities remains unclear, but the requirement for BRCA1 in *p21WAF1* activities has important implications for tumor suppressor activities of both BRCA1 and IFNγ.

The list of co-activators that interact with STAT1 is certainly much larger than that of STAT2 (see Table). Thus far, CBP/p300 is the only identified STAT2 co-activator. In the Type I IFN pathway, the prevailing view is that either STAT1α or STAT1β can interact with STAT2 and IRF9 to form ISGF3, since several lines of evidence support STAT2 as the sole provider of activating signals for ISRE-dependent transcription. However, post-translational methylation of STAT1 also appears to affect Type I IFN signaling. Whether ISGF3 complexes that contain STAT1? also recruit STAT1-specific co-activators (such as MCM5 and BRCA1), and whether these complexes induce the transcription of a slightly different profile of ISGs, remain topics of current investigations.

Conclusion

A review of the STAT cell-signaling and transcription literature suggests that the mechanisms underlying the interferon responses are becoming more complex with each new finding. Critically important for Type I IFN-dependent transcriptional functions is the carboxyl-terminal transcriptional activation domain of STAT2, but the lack of characteristic regulatory features such as the PMSP phosphoserine motif means that the ISGF3 complex employs different mechanisms to activate transcription than STATs in other signaling pathways. Why are the other components of ISGF3—STAT1 and IRF9—required for ISGF3-dependent transcription? It now appears that novel post-translational modifications of STAT1, and potentially of STAT2, may also regulate Type I IFN responses. The IRF9 component may also modulate ISGF3 cell signaling through its cytoplasmic interactions with STAT2, or through STAT-independent nuclear activities. Also, still far from complete is the list of general and gene-specific co-activator proteins that interact with the ISGF3 complex to assist in antiviral gene expression. Finding additional nuclear-binding partners for ISGF3 will undoubtedly enhance our understanding of the biochemical and molecular mechanisms by which antiviral genes are switched on and off, and provide targets for pharmaceutical design.

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Abstracts

*The following abstracts were presented by investigators at the Eighteenth Annual Samuel Bronfman Department of Medicine Research Day on October 16, 2001 at the Mount Sinai Medical Center. Most of the investigators serve in the Samuel Bronfman Department of Medicine, including those working at affiliated institutions such as The Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; and St. Joseph's Hospital and Medical Center, Paterson, NJ. Four papers were presented in the AM plenary session. Only two, identified with an *, are included as abstracts in this publication. The remaining two of these presentations at the plenary session have been published elsewhere. Abstracts from Queens Hospital Center and Jersey City Medical Center were presented as posters on Research Day held at those institutions.*

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Alcohol Research

Polyenylphosphatidylcholine (PPC) and Its Main Component Dilinoleoylphosphatidylcholine (DLPC) Attenuate Alcohol-Induced Hepatocyte Apoptosis Through Reduction in Cytosolic Cytochrome C and Caspase-3 Activity. Wen K, Mak KM, Ren C, Lieber CS. Alcohol Research Center and Section of Liver Disease and Nutrition, VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

PPC, a mixture of polyunsaturated phosphatidylcholines extracted from soybeans, attenuates hepatocyte apoptosis induced by alcohol feeding in rats, as determined by TUNEL (terminal transferase dUTP nick end labeling) assay. In the present study, we assessed whether DLPC, the most abundant phosphatidylcholine species of PPC, mediates the antiapoptotic action of PPC and whether this effect is associated with changes of cytosolic cytochrome c and alterations in caspase-3 activity, since it is known that cytochrome c released from mitochondria into the cytosol participates in the activation of caspase-3, which, in turn, triggers the apoptosis. Accordingly, rats were fed Lieber-DeCarli liquid diets containing ethanol (35% of energy) or isocaloric carbohydrate as control for 4 weeks. Another group of rats were fed the ethanol diet supplemented with PPC (3g/L) or DLPC (1.5g/L, equivalent to its content in PPC), or twice that dose. Alcohol feeding increased the incidence of hepatocyte apoptosis 6.5-fold by TUNEL assay ($5.2 \pm 0.4/\text{mm}^2$, n = 6 vs 0.8 ± 0.08 n=5 in controls, $p<0.01$). The rise was abrogated by PPC or DLPC at 1.5g/L and 3g/L. Cytochrome c in the cytosol, as measured by ELISA, rose 53.5% after alcohol feeding (64.2 ± 5.7ng/mg protein vs 41.8 ± 2.4 in controls, $p<0.05$). The increase was fully prevented by PPC or DLPC at 1.5g/L and 3g/L. Mitochondrial cytochrome c levels (about 14 times higher than those in the cytosol) did not differ significantly among treatment groups. In alcohol-fed rats, liver caspase-3 activity was 66% higher than in controls (11.5 ± 1.7 pmol AMC (7-amino-4-methylcoumarin)/mg protein/min. vs 6.9 ± 0.7, $p<0.05$). The increase was fully prevented by PPC or DLPC (1.5g/L and 3g/L). Caspase-3 activity correlated positively with the incidence of apoptosis ($p<0.001$). We have shown before that DLPC has a striking antioxidative action, which possibly accounts for its antiapoptotic effect, since oxidative stress is known to exacerbate apoptosis.

Conclusions: DLPC, the main component of PPC, accounts for its protection against the alcohol-induced apoptosis; it acts by reducing the cytosolic cytochrome c level, resulting in decreased caspase-3 activity.

DLPC Protects Against Ethanol-Induced Mitochondrial Injury in Rats. Navder KP, Lieber CS. Alcohol Research Center, and Section of Liver Disease and Nutrition, VA Medical Center, Bronx, NY, and Mount Sinai School of Medicine, New York, NY.

Chronic ethanol consumption depletes phosphatidylcholines (PC) in the membranes and hepatic mitochondria are an early target of this toxicity. Our previous studies showed that polyenylphosphatidylcholine (PPC), a 94–96% pure mixture of polyunsaturated PC extracted from soybeans, attenuates early manifestations of alcohol toxicity, including the prevention of mitochondrial liver injury. Since the main PC species of PPC (40–52%) is dilinoleoylphosphatidylcholine (DLPC), we wondered whether it is the active compound of PPC. To assess this, 26 male rats were fed the following liquid (Lieber-DeCarli) diets for 28 days: Control; Ethanol-36% of Calories (Cal) without or with PPC (3 g/1000 Cal); DLPC-1.5 (1.5 g/1000 Cal) and DLPC-3 (3g/1000Cal). As expected, ethanol feeding resulted in a 41% ($p<0.05$) decrease in the activity of mitochondrial cytochrome oxidase; this effect was prevented by PPC and also by DLPC-3 ($P<0.05$). Furthermore, chronic ethanol feeding decreased the capacity of hepatic mitochondria to oxidize palmitoyl-carnitine, as judged by a 51% decrease in respiratory control (the ratio between the ADP stimulated and non-stimulated O_2 consumption), and a 31% reduction in the ADP:O ratio (a measure of efficiency of coupling between oxidation and ATP production).

Supplementation with either PPC or DLPC-3 prevented the ethanol-induced reduction in the capacity of mitochondria to oxidize palmitoyl-carnitine ($p<0.05$). Similar effects were observed with glutamate as substrate ($p<0.05$). In conclusion, DLPC, the main PC species of PPC, fully reproduced PPC's protective effect against ethanol-induced mitochondrial liver injury and thus appears to be PPC's active component. This beneficial effect of DLPC at the initial stages of liver injury may be useful to prevent or delay the development of more severe damage.

CYP2E1 Induced by Ethanol and Its Potentiation by Beta-Carotene. Kessova I, Leo MA, Lieber CS. Alcohol Research Center and Section of Liver Disease and Nutrition, VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

Hepatotoxicity of ethanol is increased by beta-carotene in both rodents and non-human primates. Furthermore, in smokers who are also drinkers, beta-carotene increases the incidence of pulmonary cancer. The hepatotoxicity was associated with proliferation of the membranes of the smooth endoplasmic reticulum, suggesting the involvement of cytochromes P450. To verify this hypothesis, 24 weanling male Sprague-Dawley rats were pair-fed for 8 weeks liquid diets with and without beta-carotene (56.5 mg/l of diet) and with or without ethanol. As expected, ethanol increased CYP2E1 (measured by Western blots) from 66.8 ± 7.9 to 316.5 ± 26.6 absorbance units ($p<0.05$). Furthermore, beta-carotene increased the ethanol effect to 442.4 ± 37.7 absorbance units ($p<0.05$). This rise was confirmed by a corresponding increase in the hydroxylation of p-nitrophenol, a specific substrate for CYP2E1, and by the inhibition with diethyl dithiocarbamate (50 microM). The correlation coefficient between CYP2E1 content and p-nitrophenol hydroxylase activity was very significant ($r = 0.928$, $p<0.0001$; n = 24). Beta-carotene also induced CYP4A1 protein (327.5 ± 49.0 vs 158.0 ± 16.7 absorbance units) with a significant beta-carotene effect

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($p<0.01$: 2 way ANOVA). The corresponding CYP4A1 mRNA (measured by Northern blots) was increased ($p<0.05$). The combination of ethanol and beta-carotene had no effect on CYP1A1/2, CYP2B1/2, CYP2C11 and CYP3A1/2 content. Since the hepatotoxicity of ethanol has been linked to CYP2E1 induction, the potentiation of this toxicity by beta-carotene may be due, at least in part, to the increase in CYP2E1 by beta-carotene. In view of the possible carcinogenicity of CYP2E1 and CYP4A1, their induction by beta-carotene may also play a role in the greater incidence of pulmonary cancer in smokers who drink and are given beta-carotene.
In conclusion, beta-carotene potentiates CYP2E1 induction by ethanol and it also increases CYP4A1, which may explain, at least in part, the associated increased hepatotoxicity.

Polyenylphosphatidylcholine (PPC) Restores S-Adenosylmethionine (SAMe) and Corrects Alcohol-Induced Hepatic Oxidative Stress. Aleynik SI, Leo MA, Aleynik MK, Lieber CS. Alcohol Research Center and Section of Liver Disease and Nutrition, VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

Alcohol-induced liver injury caused by oxidative stress resulting in glutathione (GSH) depletion and increase of lipid peroxidation. For GSH synthesis, the rate limiting amino acid is cysteine, with S-adenosyl-L-methionine as its ultimate precursor. We showed before that PPC corrects the oxidative stress and the GSH depletion resulting from long-term alcohol consumption in non-human primates. To study whether this occurs already with early liver injury and to elucidate the mechanism involved, 32 Sprague-Dawley rats were pair-fed ethanol (36% of energy) or isocaloric carbohydrates in Lieber-DeCarli liquid diets, with or without PPC. After 2 months, there was a striking depletion of SAMe from 68.2 ± 5.1 to 36.2 ± 3.4 nmol/g ($p<0.001$) associated with a reduction in hepatic GSH from 4.95 ± 0.20 to 4.09 ± 0.08 micromol/g ($p<0.01$), and an increase from 0.24 ± 0.02 to 0.47 ± 0.07nmol/g ($p<0.001$) of 4-hydroxynonenal (4-HNE), a reliable marker of lipid peroxidation. SAMe synthetase activity remained unchanged. Feeding PPC corrected all values and, in the absence of ethanol SAMe and GSH even exceeded the control values. Neither alcohol nor PPC has an affect on SAMe synthetase activity. Phosphatidylcholines (PCs), the backbone of cellular membranes, are produced in the liver via methylation of phosphatidylethanolamine by SAMe. PPC, by providing PCs, decreases the utilization of SAMe and may thereby contribute to its restoration, with replenishment of GSH and the correction of the alcohol-induced oxidative stress. This hypothesis was corroborated by the observation that hepatic SAMe correlated positively with GSH ($r = 0.59$, $p = 0.0005$) and negatively with 4-HNE ($r = -0.64$, $p = 0.0001$).
Conclusion: Already after 8 weeks alcohol caused SAMe depletion, which was fully corrected by PPC, thereby explaining, at least in part, how PPC opposes the alcohol-induced oxidative stress and prevents the associated fibrosis.

Cardiology

Evidence for Macrophage Apoptosis as a Mechanism Regulating Tissue-Factor Expression and Plaque Growth Following Arterial Injury in ApoE -/- and C57/BL6 Wild Type Mice: R. Hutter, B.V. Sauter*, J.T. Fallon, V. Fuster, J.J. Badimon. The Cardiovascular Institute and Department of Gene Therapy and Molecular Medicine*, Mount Sinai Medical Center, New York, NY.

Background: Macrophages undergoing apoptosis are considered contributing to progression of atherosclerotic lesions. Tissue factor is a key cell-mediated activator of extrinsic coagulation-cascade and can induce thrombus formation.
Methods: In the present study, we examined the role of macrophage apoptosis on plaque growth by comparing neointima formation in ApoE -/- (n=10) and C57/BL 6 wild type mice (n=23) in a model of femoral arterial denudation injury.
Results: Arterial injury resulted in significantly increased neointima formation in ApoE -/- mice at 4 weeks compared to wild type mice (4.84 ± 1.26 mm^2 x 10^{-2} vs. 0.73 ± 0.03 mm^2 x 10^{-2}; $P<.01$). Apoptotic macrophages and foam cells as detected by caspase-3 expression, characteristic morphology and positive staining for MOMA-2 were found only in lesions of ApoE -/- mice and accounted for up to 33 ± 6 % of intimal cells at 4 weeks after arterial injury compared to less than 0.5 % apoptotic cells in neointima of wild type mice ($P<.01$). Importantly, neointima size significanly correlated with the content of apoptotic macrophages in neointima ($r = 0.64$, $P<0.01$). In addition, apoptotic macrophages were directly associated with increased cellular tissue factor expression as well as reduced alpha-actin expression in neointima of ApoE -/- mice ($r = 0.97$, $P<0.01$, $r = -0.75$, $P<0.01$, respectively).
Conclusions: Apoptosis of macrophages and enhanced expression of cellular tissue factor in neointima correlated with increased plaque growth and change of neointima to an unstable plaque-like phenotype. These findings point to an important role of programmed cell death of macrophages in modulating arterial lesion biology and controlling thrombogenic properties of intimal lesions following arterial injury.

Decreased Neointima Formation and Vascular Wall Neovascularization after VEGF-165 Overexpression in a Mouse Model of Arterial Injury. R. Hutter, B. Sauter*, C. Wolinsky, V. Fuster, S.L.C. Woo*, J.J. Badimon. The Cardiovascular Institute, and Department of Gene Therapy and Molecular Medicine*, Mount Sinai Medical Center, New York, NY.

Background: Human VEGF-165 as strong promotor of endothelial cell growth has been contradictorily shown to either *de*crease or increase neointima formation in different animal models. After arterial denudating injury endothelial cells play a dual role in regulating neointima formation either *via* re-endothelialization of denuded luminal surface (negative feedback) or *via* ingrowth of adventitial vasa vasorum (positive feedback). Systemic levels of VEGF-165 might therefore modulate both processes simultaneously.
Methods: Using a mouse model of arterial injury we, therefore, examined in parallel the effects of VEGF-165 overexpression on neointima formation, re-endothelialization and vascular wall neovascularization. C57/BL6 mice underwent femoral arterial denudation and received either recombinant adenovirus expressing VEGF-165 (n = 14) at two dosages (10^{10} or 10^9 viral particles) or control adenoviral vector (n = 17) by jugular vein injection.
Results: VEGF-165 gene transfer at 10^{10} viral particles (high dose) resulted in significantly elevated VEGF-165 serum levels at 1 week and led to a strong reduction of neointima formation at 4 weeks after arterial injury compared to control vector treatment (2.5 ± 1.4 *vs.* 8.4 ± 3.5 x 10^{-3} mm^2, $P<0.01$). VEGF-165 gene transfer at 10^9 viral particles (low dose) did not change neointima formation after injury compared to control adenoviral vector. Re-endothelialization was nearly completed at 4 weeks and was not changed by any VEGF-165 treatment compared to control group (84 ± 8% vs. 84 ± 12%, $P>0.05$). However, a more than two-fold *reduction* of arterial wall neovessel content was found in high dose VEGF-165 treated animals compared to control group (0.6 ± 0.4 *vs.* 1.6 ± 0.8%, $P<0.05$). At high dose VEGF-165 treatment an increased mortality during first week was observed.
Conclusions: High dose VEGF-165 gene therapy is effective at inhibiting arterial lesion formation following mechanical endothelial injury. The therapeutic effect of VEGF-165 is probably mediated by accelerated early luminal endothelial regrowth and reduced late arterial wall neovascularization pointing to the luminal endothelium as a strong negative regulator of neointimal and arterial wall neovessel growth. The approach of using VEGF-165 systemically to enhance luminal endothelial cell regeneration is, however, limited by a small therapeutic window. Therefore, to sucessfully inhibit neovascularization and neointima formation at multiple sites additional, similarly acting molecules with better safety have to be used.

*** Is There a Role for "Limited," Rapid, Bedside Hand-Held Echostethoscope in the Surgical Intensive Care Unit?** Ben Cohen, Medical Student; Thomas Dorantes, Medical Student; Nagaraj Hosakote, M.D. Surgery; Lori B. Croft, M.D. Cardiology; Elie Portnoy, Student*; Anthony Manasia, M.D. Surgery; John Oropello, M.D. Surgery; Ernest Benjamin, M.D. Surgery; Roopa Kohli-Seth, M.D. Surgery; Rosanna DelGiudice, R.N. Surgery; Jerry Hufanda, R.N. Surgery; and Martin E. Goldman, M.D. Cardiology. Mount Sinai Medical Center, New York, NY and *Yeshiva University, New York, NY.

Patients in the Surgical Intensive Care Unit (SICU) are frequently unstable. The clinical exam is frequently not definitive and invasive procedures, such as a pulmonary artery catheter are required to indirectly assess left ventricular filling. Studies have questioned the safety of PA catheters. Echocardiograms provide a direct, real time assessment of left and right ventricular size and function. Unfortunately, the expertise to perform an echo is limited to specially trained technologists and cardiologists. Recently, small, inexpensive, hand-held echocardiograph systems have been introduced, which may serve as echo-stethoscopes for bedside assessment of LV function.
Hypothesis: A "limited" echo (2–4 views, without Doppler or m-mode) to assess LV size and function, exclude significant valvular disease and pericardial effusions, would provide valuable information in intensive care patients.
Methods: After clinical assessment of the patients in the SICU clinical status, cardiac function and volume status were estimated. Patients then underwent a "limited" echo by surgical intensivists and medical students with a Sonoheart® (Sonosite, WA). After the studies were reviewed and results confirmed by an echocardiologist, the intensivist determined if the echo changed their clinical assessment of the cardiac status (function and volume) or changed therapeutic management.
Results: A diagnostic echo was possible in 59/61 (97%) patients in the SICU. Of the remaining 59 pts, the limited echo changed the cardiac diagnosis in 27/59 (46%) and changed management in 16/59 (27%).
Conclusion: The "limited" echo-stethoscope provided significant new information and changed therapeutic management in a significant number of patients. Studies were performed by non-cardiologists to confirm that this technology can potentially be integrated to the routine bedside examination of patients.

Hand-Held Ultrasound Machines: Are They Ready for Everybody? Thomas Dorantes, Medical Student; Ben Cohen, Medical Student; Nagaraj Hosakote, M.D., Surgery; Lori B. Croft, M.D., Cardiology; Elie Portnoy, Student*; Ravindra Kodali, M.D., Surgery; Anthony Manasia, M.D., Surgery; John Oropello, M.D., Surgery; Ernest Benjamin, M.D., Surgery; Roopa Kohli-Seth, M.D., Surgery; Rosanna DelGiudice, R.N., Surgery; Jerry Hufanda, R.N., Surgery; and Martin E. Goldman, M.D., Cardiology. Mount Sinai Medical Center, New York, NY and *Yeshiva University, New York, NY.

Most recent technological advances in medical imaging have produced huge and expensive equipment (CT, MRI, PET).

However, though hand-held, inexpensive ultrasound systems have been developed but have been evaluated only by physicians and/or technicians with years of experience. The promise of these machines should be to empower all physicians with the skill of performing a limited echo at the bedside, as an "echo-stethoscope."

Hypothesis: Medical students and physicians without prior experience can obtain and interpret diagnostic, "limited" echocardiograms on a hand-held ultrasound device.

Methods: After they had a limited tutorial with practical experience, 2 fellows in Surgical Intensive Care Unit and 2 first year medical students performed a "limited" echo in 61 patients in the Surgical Intensive Care Unit with a new hand-held ultrasound system, the Sonoheart® (Sonosite, WA). Studies were performed and stored on video tape. Each study was reviewed and repeated by an experienced echocardiologist to determine if the intensivists' and students' echo images were adequate to be diagnostic and if they interpreted the images correctly.

	Intensivist	Med Student
Diagnostic Images	83%	97%
Interpreted Correctly	66%	78%

Results: The echocardiologists felt the H-H echo was diagnostic in all but two patients (97%). Of the remaining 59 patients, both intensivists and students were able to obtain diagnostic images in most patients and interpreted them fairly well. Students spent more time in performing and interpreting echo's which may explain the difference with intensivist performance.

Conclusion: Small hand-held, echocardiographic systems enable medical students and non-cardiologists to perform and interpret accurate limited echocardiograms. Implications of this study may support formally educating medical students and physicians to utilize echo-stethoscopes at the bedside.

Atherosclerotic Lesional Macrophage Foam Cell RNA Can Be Selectively Procured by Laser Capture Microdissection for Analysis of Cell-Specific Gene Expression. Trogan E.*, Dansky H.M.[§], Choudhury R.P.*, Rong J.X.*, Breslow J.L.[§], Fisher, E.A.*. *The Zena & Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY; [§]Laboratory of Biochemical Genetics and Metabolism, The Rockefeller University, New York, NY.

Background: Macrophage lipid-laden foam cells contribute to the formation of atherosclerotic lesions. The ability to selectively measure macrophage foam cell gene expression in atherosclerotic vessels is limited due to the presence of smooth muscle cell, lymphocyte, and endothelial cell derived mRNA transcripts in homogenized samples. To overcome this limitation, we used laser capture microdissection (LCM) to selectively procure RNA from lesional macrophages.

Methods: Frozen serial aortic root tissue sections from 20 week old chow fed apolipoprotein $E^{-/-}$ mice were immunostained for macrophage-specific CD68/Macrosialin by a rapid (~15 min) protocol. Alternating sections from each animal were divided into two groups, with either entire sections processed for RNA isolation (analogous to isolation from whole tissue), or just the CD68-positive areas isolated by LCM. Total RNA was extracted by the guanidinium isothiocyanate and phenol-chloroform method and quantified by a sensitive nucleic acid-dye binding assay (Ribogreen). Using real-time quantitative RT-PCR, mRNA levels of 3 genes were determined; *CD68*, a macrophage specific marker, *alpha-actin*, a smooth muscle cell marker, and *cyclophilin A*, a normalizing gene.

Results: LCM of the CD68-positive cumulative cross-sectional area (223,662 (µm^2 , from 30 sections, each 6 (µm thick) yielded 3.6 ng of total RNA. CD68 expression in the LCM-extracted RNA was significantly higher than in that extracted from entire sections when adjusted either to RNA mass or to cyclophilin A levels (fold enrichment: 30.1 ± 4.9 or 37.6 ± 6.2, respectively). In contrast to whole section-extracted RNA, alpha-actin RNA was not detectable in lesional macrophage RNA, demonstrating the high purity of the isolated lesional macrophage RNA. The integrity of the LCM RNA sample was demonstrated by conventional RT-PCR of a 450 bp GAPDH fragment.

Conclusion: LCM provides a means for selectively obtaining macrophage foam cell RNA from lesions and will significantly improve *in vivo* gene expression analysis from heterogeneous atherosclerotic tissue. GCO# 98-221

Human Apolipoprotein AI Suppressed Atherosclerosis without Elevating Plasma HDL Cholesterol in LDL Receptor-Knockout Mice on Western-Diet. James X. Rong*[§], M. Haghpassand[†], R.P. Choudhury*, V.I. Elmalem*[§], A.L. Carrelli*[§], E. Trogan*[§], J.T. Fallon*[§], and E.A. Fisher*[§]. *The Zena & Michael A. Wiener Cardiovascular Institute, [§]Department of Medicine, Mount Sinai School of Medicine, New York, NY; [†]Pfizer Global Research Laboratories, Groton, CT.

Background: Expression of human apolipoprotein AI (hAI) transgene has been shown to retard atherosclerosis progression in apoE knockout mice. To test this in another mouse model of atherosclerosis and to compare the relative effects on lesion progression of HDL composed of human vs. mouse apoAI (mAI), studies were performed in LDL receptor knockout (LDLrKO) and hAI/LDLrKO mice.

Methods and Results: At weaning, LDLrKO mice with or without the hAI transgene were fed Western diet, and atherosclerosis was assessed in the aortic root after 10 (n = 4 in each genotype) or 15 (n = 6 in each genotype) weeks. In hAI/LDLrKO mice, mean plasma human apoAI level was 208+/-30 mg/dL, but mouse apoAI was suppressed compared to that in LDLrKO mice (10+/-4 vs. 195+/-70 mg/dL, respectively, P<0.05). The total apoAI, HDL cholesterol (HDL-C), and total cholesterol were comparable between the two groups. There was also no difference in plasma lipoprotein FPLC profiles. Despite the comparable HDL-C levels, there was significant suppression of lesions in hAI/LDLrKO mice compared to LDLrKO mice after 10 weeks (0.02+/-0.01 vs. 0.11+/-0.03, respectively, P<0.03) and 15 weeks (0.16+/-0.04 vs. 0.31+/-0.04 mm^2, respectively, P<0.03) on Western diet.

Conclusions: Expression of hAI suppressed diet-induced atherosclerosis in LDLrKO mice without changing plasma levels of apoAI or HDL-C. Therefore, HDL primarily composed of hAI appears to be functionally superior to native mouse HDL as an atheroprotective agent.

F-18 Fluorodeoxyglucose Uptake in Human Thoracic Aortas Assessed *In Vivo* by Positron Emission Tomography. J. Machac, Z. Zhang, R. Nunez, W. Chen, H. Macapinlac, and S. Larson. Mount Sinai School of Medicine, New York, NY and Memorial Sloan-Kettering Cancer Center, New York, NY.

Background: Our laboratory (Vallabhajosula et al., Zhang et al., Helft et al) has previously demonstrated increased F-18 fluorodeoxyglucose (FDG) uptake in the thoracic aortas in hypercholesterolemic rabbits in vivo and ex-vivo as a function of atherosclerotic plaque macrophage burden. FDG uptake in human atherosclerosis has not yet been studied. We set out to determine the prevalence of increased FDG uptake in human thoracic aortas and relate it to age and gender.

Methods: We retrospectively studied 50 consecutive patients undergoing whole body FDG positron emission tomography (PET) imaging for diagnosis and staging of tumors using a GE ADVANCE PET scanner with iterative reconstruction and segmented attenuation correction. The patient population consisted of 32 men and 18 women, mean age 56 years (range 15–82). FDG uptake in the thoracic aortic wall was assessed objectively by measured maximal SUV in the most prominent uptake regions. High uptake (SUV > 2.5) prevalence was related to age and gender using the chi-square test.

Results: 29/50 (58%) patients had foci of increased uptake (SUV>2.5), two visually very striking, mostly in the aortic arch. Uptake was strongly related to age (p<0.001) and weakly related to gender (p = 0.09).

Conclusion: The prevalence of increased FDG uptake in human thoracic aortas is common and increases with age and male gender. Noninvasive measurement of FDG uptake in human aortas by PET is a potential tool in the *in vivo* assessment of aortic plaque macrophage activity. It needs to be evaluated for prediction of CAD severity and of future clinical events related to ASHD.

FDG Uptake Gender	Age (yrs)			
SUV	< 55	>55	Male	Female
SU SUV <2.5	13	8	10	10
SUV >2.5	29	18	22	8

F-18 FDG Uptake in Human Thoracic Aortas and Correlation with Clinical Risk Factors. J. Machac, Z. Zhang, O.D. Almeida, W.T. Chen, B.R. Krynyckyi, and C.K. Kim. Mount Sinai School of Medicine, New York, NY.

Background: Our laboratory (Vallabhajosula et al., Zhang et al., Helft et al.) has previously demonstrated increased F-18 fluorodeoxyglucose (FDG) uptake in the thoracic aortas of hypercholesterolemic rabbits *in vivo* and *ex-vivo* as a function of atherosclerotic plaque macrophage burden. Recently, we found that FDG uptake in human atherosclerosis (AS) is correlated with age. We set out to determine the prevalence of increased FDG uptake in human aortas and relate it to risk factors for CAD.

Methods: We studied 57 patients who were referred to MSSM for routine clinical whole body FDG oncological positron emission tomography (PET) imaging using a GE ADVANCE PET scanner with iterative recon-

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struction and segmented attenuation correction. The patients were questioned for risk of CAD. The patient population consisted of 24 men and 33 women, mean age 60.6 years, ranging from 23 to 86. FDG uptake in the thoracic aortic wall was assessed objectively by measured maximal SUV in the most prominent uptake regions. We assessed relationship between high uptake (SUV > median) prevalence and clinical risks using the chi-square test.
Results: The median SUV was 2.0. 28/57 (49%) patients had foci of high uptake (SUV>2.0), mostly in the aortic arch. Uptake was significantly related to obesity (p = 0.014) and hyperlipidemia (p=0.043), and weakly related to diabetes (p = 0.08), but not related to gender, smoking, and family history of premature CAD.
Conclusion: Increased FDG uptake in human thoracic aortas is common and the prevalence increases with several risk factors for CAD. Noninvasive measurement of FDG uptake in human aortas by PET is a potential tool for the *in vivo* assessment of aortic plaque macrophage activity. It needs to be evaluated for prediction of CAD severity and of future clinical events related to ASHD.

The Digital Echo Lab Has Arrived: Comparison of Digital vs. Video Review in 100 Patients. Jennifer Pennimpede, RDCS, Cardiology; Lori B. Croft, MD, Cardiology; Eric H. Stern, MD, Cardiology; Tamanna Nahar, MD, Cardiology; Samantha Buckley, RDCS, Cardiology; Robert Shapiro, MD, Cardiology; and Martin E. Goldman, MD, Cardiology. Mount Sinai Medical Center, New York, NY.

Videotape (Video) has been the standard medium for reviewing and archiving echo studies. Recently, digital archiving has been proposed as the new, improved method of echo review and storage. While videotape can record continuously, digital loops must be stored individually throughout the exam (on non-streaming systems). Thus, to determine whether digital reading would be equivalent in quality and review time to video, we acquired and read 100 routine, random patient studies acquired on both video and digital. We used a commercially available system, KinetDx® (Acuson) with 2 cardiac cycles/loop. The video and digital studies were read in alternating sequence (51 digital read first). The time for reading each mode, comparison of quality, missed diagnoses and loops stored by tech and edited down by M.D. were recorded.
Results: The major referring diagnosis was to assess LV function (58%). When read first, the video study took 6.25 ± 1.98 minutes to review, compared to 3.01 ± 1.29 minutes for the digital to be read and edited (p<.0001). When read second, the video study took 4.75 ± 1.80 minutes compared to 2.38 ± 1.14 minutes for digital (p<.0001). There were 3 major diagnoses missed by video, 6 by digital (p = N.S.). Irregular rhythms created gating problems for digital acquisition, even if we defaulted to time acquisition. The average number of loops stored by a technician was 63 ± 20 which was reduced for storage by 28% while the M.D. reviewed the study. Therefore, the total time for digital echo reading and editing for archiving took less than 50% of the time to read video. Study quality was equivalent. Thus, digital acquisition and editing on a commercially available system can significantly speed reading time without loss of quality.

*** The Role of Troponin-I in Chronic Hemodialysis Patients.** Zafar MU[a], Farkouh ME[a], Robbins MJ[a, b], Shimbo Da, Davidson K[a], Volate Rb, Halperin JL[a], Epstein EM[b], Patel M[b], Talor Z[b], Chesebro Jh[a]. [a]Mount Sinai Medical Center (Cardiovascular Institute), NY[b] St. John's-Queens Hospital (Department of Medicine), NY.

Purpose: Patients on hemodialysis have a high mortality rate primarily due to cardiovascular events (1, 2). Evidence suggests that troponin-I (cTnI) levels may have a role in predicting these adverse cardiovascular events (3, 4).
Subjects and Methods: All chronic hemodialysis patients at two teaching hospitals in New York were followed prospectively for cardiovascular events after screening for baseline cardiovascular risks and cTnI. Patients who had suffered any acute coronary event within the preceding 30 days were excluded from the study.
Results: A total of one hundred and thirty seven patients were enrolled (mean age 58 years, 52% males). Of these 7.3% (10/137) had elevated cTnI levels when a cutoff of >1.0ng/ml was used. Controlling for other known cardiovascular risk factors (age, diabetes, hypertension, family history of coronary artery disease, smoking, sex, CPK, homocysteine), at 6 months 40% of patients with cTnI>1.0ng/ml had an event while 8% of those with normal cTnI levels had an event (OR = 9.7, CI = 1.9–50.6, p<.01)). At one year the event rate was 60% vs. 16.5% respectively (OR = 4.1, CI = 1.5–11.5, p<.01).
Conclusion: Our study of stable chronic hemodialysis patients shows a high incidence of cardiovascular events in all subjects, especially in those with elevated baseline cTnI levels. This finding was found to be significant at both 6 months and at one year. All chronic hemodialysis patients are at a significantly increased risk for future cardiac events and should be managed with aggressive risk factor modification. However, the additional cardiac risk conferred by an elevated cTnI level in this population may warrant an even more aggressive approach and this should be the basis for further studies.

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Clinical Experience with Radiofrequency Catheter Ablation for Atrial Flutter: Is There a Point of Diminishing Return of Energy Delivery? Z. Curillova, C. Irmiere, N.G. Tullo. Dept. of Medicine, St. Joseph's Regional Medical Center, Paterson, NJ.

Introduction: Radiofrequency (RF) catheter ablation is an interventional procedure that is effective in eliminating atrial flutter. RF electrical energy is delivered to the tricuspid annulus/inferior vena cava isthmus to create bi-directional conduction block across this critical part of atrial flutter reentry circuit. However, complete block cannot be accomplished in some cases. We attempted to analyze our experience with this procedure, to determine how much energy was sufficient to successfully ablate the tricuspid-caval isthmus (CTI).
Methods: A retrospective analysis of catheter ablations for atrial flutter at St. Joseph's Hospital and Medical Center between 05/96 and 12/00 was performed. Successful and unsuccessful outcomes were analyzed, with respect to demographic characteristics.

The temperature, electrical power, and duration of each RF burn were examined. The total RF energy (in joules) and the number of burns delivered were compared between successful and unsuccessful procedures. Statistical analysis using Student's T-Test was used.
Results: A total of 33 patients (28 male, 5 female), mean age 61.6 ± 13.6 years were included in the analysis. Of these, 22 ablations (67%) resulted in successful CTI block and 11 (33%) were unsuccessful. Over time the success rate improved. There were no significant differences in mean temperature, power, or duration of the burns between successful and unsuccessful ablation. The mean total energy delivered in successful ablation was 25.9 ± 15.3 kJ, while the energy delivered in unsuccessful ablations was 50.8 ± 30.7 kJ (p = 0.025). A mean of 24 ± 13.3 burns were made during successful ablations, compared with 50 ± 27 burns in unsuccessful ablations (p = 0.011). No successful procedure required more than 50 burns of 60 kJ of energy delivered.
Conclusions: (1) The success rate of RF catheter ablation for common atrial flutter increased over time, which is likely related to the experience of the operators and improvement in mapping/catheter technology. (2) Significantly higher energy delivery and a greater number of burns were seen in unsuccessful cases, reflecting persistent attempts at creating complete CTI block. (3) It appears that delivering more than 50 burns or 60,000 J of energy would be unlikely to result in successful ablation, possibly due to the development of edema in the CTI. In that event a repeat ablation procedure is suggested after the edema has resolved.

Clinical Immunology

Human B Cell Differentiation Factor, 446BCDF, Also Is B Cell and Monocyte Directed Chemokine. Yande Kuang and Lloyd Mayer. Division of Clinical Immunology, Department of Medicine, Mount Sinai Medical Center, New York, NY.

B cell differentiation factor (BCDF), 446BCDF, derived from anti-CD3 mAb (446) stimulated human T cells is a 44Kda cytokine which is a potent inducer of Ig secretion by SAC activated human B cells. We have previously reported that 446BCDF is also chemotactic for B cells and monocytes, but not for T cells and neutrophils. Both the immunoglobulin inductive activity and chemotactic activity were found only in fractions with higher molecular weight (>30Kda) and were blocked by anti-446BCDF mAb, 929. The chemotactic activity of 446BCDF pre-absorbed with monocytes was significantly reduced for both B cells and monocytes, suggesting that chemotaxis was induced by a single cytokine. Only two of the known chemokine receptors (CCR2 and CXCR4) are expressed on both B cells and monocytes. Monocyte migration induced by 446BCDF was not inhibited by an anti-CXCR4 mAb. Furthermore, human B cells did not respond to MCP-1 (CCR2 ligand) in a chemotaxis assay. Therefore, it appears that both CXCR4 and CCR2 are not involved in 446BCDF induced cell migration. To confirm these data in a competitive assay, we added either optimal concentrations of SDF-1a (CXCR4 ligand), MCP-1 or MIP-1a into the upper chamber along with monocytes and measured chemotactic activity of 446BCDF in the lower chamber. SDF-1a, MCP-1 and to a lesser extent MIP-1a blocked cell migration to the lower well. However when these chemokines were added to both the upper and lower chambers (eliminating the gradient), monocytes migrated towards the lower chamber containing 446BCDF. These data support the contention that 446BCDF binds to a distinct chemokine receptor and is in itself a distinct chemokine.

Endocrinology

More on the Role of HLA Genes in the Susceptibility to Autoimmune Thyroid Disease in 102 Families. Y. Ban, Y. Tomer, ES. Concepcion, DA. Greenberg*, and TF. Davies. Division of Endocrinology, Diabetes, and Bone Diseases, Department of Medicine and *Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The autoimmune thyroid diseases (AITDs), comprising Graves' disease (GD) and Hashimoto's thyroiditis (HT), are complex diseases which result from an interaction between predisposing genes and environmental triggers. Population-based case control studies have shown a consistent association of GD with human leukocyte antigen (HLA)-DR3 in Caucasian populations. HLA association studies in HT have shown different alleles and have not been as consistent as in GD. Linkage studies of HLA with AITD have been mostly negative. Recently, only one study showed weak evidence for linkage with HLA in GD using non-parametric analysis of sib-pairs (Vaidya et al., 1999). The aim of our study was to perform detailed linkage and association analyses of the HLA region in AITD in order to further resolve the previous conflicting data. We studied 102 multiplex, multi-generational, AITD families for linkage with the HLA region. We generated a map of the region as follows: (Inter-marker distances are in centimorgans.) Telomere-D6S276-3.7-D6S464-2.9-HLA-A-1.3-HLA-C-0.05-D6S439-0.15-HLA-B-1.15-HLA-DRB1-0.01-D6S273-0.22-HLA-DQA1-0.24-TNF alpha-1.2-D6S1610-Centromere. The analysis showed negative LOD scores throughout the region. The maximum LOD scores at marker D6S273 (the closest to HLA-DRB1) were −2.4 for GD, -0.4 for HT, and −3.8 for AITD (GD + HT). These results confirmed earlier studies by us, and others, showing no evidence for linkage of HLA to AITD. We then performed case-control association analyses using the 99 Caucasian probands from our families (60 with GD and 39 with HT) and 135 sex- and age-matched Caucasian controls. As previously reported, we found that DR3 was associated with Caucasian GD probands ($P = 0.00032$; chi^2 = 12.9; RR = 3.42). We also found that DR4 was associated with Caucasian HT probands ($P = 0.043$; chi^2 = 4.09; RR = 2.13). We found no evidence for linkage to the HLA region when analyzing only DR3 positive families ($n = 34$). We concluded that 1) HLA genes made only a small contribution to the overall genetic susceptibility to AITD, because they were not linked; 2) HLA-DR3 conferred an increased risk of developing GD, but it was most likely only a minor modulating gene that may increase susceptibility to GD.

The Thyroglobulin Gene Is a Major Gene for Autoimmune Thyroid Disease. Y Tomer, DA Greenberg[1], ES Concepcion, and TF Davies. Division of Endocrinology and Metabolism, Department of Medicine, and [1]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Abundant epidemiological data point to a strong genetic influence on the development of autoimmune thyroid disease (AITD). We have been mapping the susceptibility genes for AITD using whole genome screening. In our first genome scan of 56 families we identified 7 loci which were linked with AITD. In two of these loci there was evidence for putative susceptibility genes (CTLA-4 on chromosome 2q33 and CD40 on 20q11). We have now extended our studies to a larger group of 102 multiplex, multigenerational, families (540 individuals). A whole genome screen using these 102 families showed strong evidence for linkage at chromosome 8q24 with a maximum 2-point LOD score (MLS) of 2.8 (NPL = 2.2). This MLS was obtained with heterogeneity (~45% of the families were linked). Multipoint analysis showed a 12 cM interval giving a maximum heterogeneity LOD score of 3.5 between markers D8S514 and D8S284. This interval contained the thyroglobulin (Tg) gene. In order to analyze whether the Tg gene could be the AITD susceptibility gene on 8q24 we performed BLAST searches through chromosome 8 sequence databases and identified two new microsatellites inside the Tg gene (designated Tgms1 and Tgms2). Tgms1 was located in intron 10 of the Tg gene, and Tgms2 in intron 27. Allelic analysis showed that Tgms2 was much more informative with a heterozygosity index of 0.79, and was, therefore, used for further analyses. The Tgms2 microsatellite showed strong evidence for linkage with AITD (MLS = 2.9, NPL = 2.2), confirming that the Tg gene was linked to AITD. We then used Tgms2 to test whether the Tg gene demonstrated association with AITD in addition to linkage. We compared 190 Caucasian GD patients (64 of them probands from our families) to 134 age and sex-matched Caucasian controls. The analysis showed an association of GD with Tgms2. Allele #3 (336 bp) was present in 30% of the patients and in 22% of the controls ($p = 0.05$, relative risk = 1.4). When we analyzed only the probands from the linked families we found that 40% of them had allele #3 versus 22% in the controls ($p=0.004$). We concluded that the thyroglobulin gene was a major AITD susceptibility gene because it was linked and associated with AITD. Alterations in the Tg gene could theoretically predispose individuals to develop AITD by changing the antigenicity of Tg as demonstrated in many studies.

Cell Biology of the TSH Receptor: Capping and Multimerization within Intact Cells Shown by Fluorescence Resonance Energy Transfer (FRET). R. Latif, P. Graves, and T.F. Davies, Division of Endocrinology, Diabetes and Bone Diseases, Mount Sinai School of Medicine, New York, NY.

We previously showed that human TSHRs, from detergent solubilized thyroid membranes existed as cleaved " alpha and beta$ subunits plus some uncleaved holoreceptors. These were present as monomers, dimers, and higher order complexes, some of which were disulfide bonded (Endocrinology 1997; 137:3915-3920). To facilitate such studies, we expressed the human TSHR as a fusion protein linked to amino terminus of Green Fluorescent Protein (GFP). Chinese Hamster Ovary (CHO) cells expressing hTSHR-GFP fusion proteins demonstrated plasma membrane localization observed by plasma membrane labeling with a red lipophilic carbocyanine derivative(CM-Dil) generating a yellow cell surface membrane fluorescence upon co-localization with GFP. Furthermore, the fluorescent receptor was functional as evidenced by TSH-induced generation of cAMP with a maximum stimulation index of >40, suggesting appropriate internal trafficking and correct folding of the recombinant hTSHR-GFP construct. In addition, we observed time- and dose-dependent capping of the receptor following TSH stimulation. We next used FRET to examine the proximity of individual hTSHRs on the CHO plasma membrane. hTSHR linked to GFP variants (red-RFP & yellow-YFP) were used as donor and acceptor molecules. FRET data using single transfectants fused by polyethylene glycol (PEG-1500) showed a transfer of energy from YFP to RFP. This confirmed the close proximity of the tagged receptors and further suggested the existence of functionally relevant dimers and/or multimers on the surface of these transfected cells. To confirm this observation, hTSHR carrying a c-myc epitope tag on its carboxyl end was transfected into TSHR-GFP cells for co-immuno-precipitation experiments. The presence of hTSHR-GFP in anti-myc immunoprecipitates was confirmed by using GFP antibody to probe the immunoblot. A fusion protein of 85 kD, comprising GFP (27KD) fused to a TSHR-$ fragment of 58KD, indicated the presence of $myc-$GFP dimers (and/or higher order complexes) in the co-immunoprecipitates. The absence of TSH holoreceptor in the co-immunoprecipitates further suggested that cleavage was essential for hTSHR complex formation. These data demonstrated that the dynamic life cycle of the TSHR involved expression, capping, and multimerization. However, the function of these higher order complexes remains to be determined.

Gastroenterology

Divergent Effects of Chronic Nicotine Administration on Jejunitis and Colitis in Interleukin 10-Deficient Mice. Eliakim R, Fan Q, Nimmagadda K, Babyatsky MW. Divisions of Gastroenterology. Rambam Medical Center, Haifa, Israel, and Mount Sinai School of Medicine, New York, NY.

Cigarette smoking alters the course of inflammatory bowel disease (IBD).

Smoking protects against ulcerative colitis (UC), but aggravates or has no effect on Crohn's disease (CD). While the etiology of this discrepancy remains unclear, differences between location of involvement in UC and CD have not been examined in these studies. We have previously shown that nicotine (12.5mg/ml), a main active ingredient in cigarette smoke, protects against colonic injury but exacerbates jejunal injury induced by iodoacetamide in rats. The aim of the current study is to examine the effects of nicotine administration on the course of jejunitis and colitis in interleukin (IL) -10 deficient (KO) mice.

Methods: Male C57/Bl6 IL-10 KO and wildtype (WT) mice were given nicotine (12.5mg/ml) in their drinking water at age 12-14 weeks when they had developed clinical signs of IBD. Sex and age-matched control mice received tap water alone. All mice were sacrificed after two weeks of treatment. Whole tissue sections of jejunum, proximal and distal colon were separated and examined by macroscopic and histologic score. RNA was prepared by Trizol reagent purification; Northern blots were examined for somatostatin (SST) and intestinal trefoil factor (ITF) gene expression, two peptides with protective properties in experimental IBD; blots were reprobed with b-actin and MUC2 as RNA/mucin expression controls.

Results: At sacrifice at 14–16 weeks, IL-10 KO untreated control mice developed both jejunitis (macroscopic score (macro) = 1.4 + 0.5, microsocpic score (micro) = 2.0 + 0.2) and colitis (macro = 2.0 + 0.2, micro = 5.9 + 0.9). IL-10 KO mice treated with 2 weeks of nicotine had significantly reduced macro 1.4 + 0.6) and micro (2.2 + 0.15) colonic scores ($p=0.01$). In contrast, the jejunum was more severely damaged with macro scores 2.6 + 0.4 and micro 4.0 + 0.3 ($p = 0.01$). Nicotine significantly increased both SST and ITF mRNA expression in colon but not in jejunum; no effect was noted on MUC2 or b-actin mRNA expression.

Conclusions: 1. Two weeks of nicotine administration leads to contrasting effects on jejunal and colonic inflammation in IL-10 KO mice. 2. Nicotine ameliorated inflammation in the colon, which was associated with enhanced expression of two protective peptides. 3. Regional effects of nicotine on gut inflammation may, at least partially, explain divergent effects of cigarette smoking seen in UC and CD.

Somatostatin Improves Enterocolitis in IL-10 Deficient Mice. Nimagadda K. Eliakim R. Fan Q. Zhang J. Babyatsky MW. GI Divisions. Rambam Hospital. Haifa. Israel; and Mount Sinai School of Medicine, New York, NY.

We have previously demonstrated that local neural somatostatin (SST) is markedly deficient in interleukin (IL)-10 deficient (KO) mice, even prior to the appearance of enterocolitis (Gastroenterology 1998; 114:A1004). Further, IL-10 administration in IL-10KO mice prevents or ameliorates the enterocolitis and restores SST levels to those seen in wildtype non-inflamed control mice. Aim: to determine if SST treatment alters the IBD phenotype in IL-10 KO mice.

Methods: Male C57Bl/6 IL-10 KO mice from Jackson laboratories were housed in conventional facilities until age 16-18 weeks of age, when they developed evidence of IBD (weight loss, bloody diarrhea, or rectal prolapse). IL-10KO mice or wildtype mice (20 mice/group) were treated with continuous SST (2.5 mg/day) or saline infusion by Alzet miniosmotic pump for 14 days. Mice were weighed every 2 days; no mice expired during the treatment. At sacrifice, serum was obtained for SST radioimmunoassay (RIA). Equivalent whole tissue sections were obtained from jejunum, right colon, and left colon and placed in formaldehyde for tissue sections or Trizol buffer for RNA preparation. RNA was examined by Northern blot analysis for cytokine expression and re-probed with b-actin for RNA loading control vy scanning densitometry.

Results: SST infusion resulted in high levels of serum SST by RIA in both the IL-10KO mice and wildtype controls. By the end of two weeks, the wildtype mice treated with SST or saline gained similar amounts of weight (2.12 + 0.6 vs. 1.98 + 0.5). IL-10 KO mice treated with SST gained a similar amount of weight to the two groups of wildtype mice (1.78 + 0.7g). In contrast, IL- 10 KO mice treated with saline lost weight (0.25g + 0.5g; $p < 0.001$). No wildtype mice demonstrated any signs of enterocolitis, either grossly or microscopically. IL-10 KO mice had significantly higher macroscopic (3.4 + 0.9) and microscopic (5.0 + 1.2) colonic scores compared to SST-treated mice (macro:1.4 + 0.6) (micro:2.0 + 0.9) ($p<0.001$). Similar results were seen in the jejunum. Northern blot analysis demonstrated significantly lower levels of IL-8, MCP-1 and TNFa in IL-10 KO mice treated with SST compared to those treated with saline. However, SST did not alter levels of these cytokines in SST-treated or control wildtype mice.

Conclusions: 1. SST significantly ameliorates the enterocolitis seen in IL-10 KO mice. 2. SST reduces pro-inflammatory cytokine mRNA expression in IL-10 KO mice but not in non-inflamed controls. 3. SST acts as an anti-inflammatory mediator in IL-10 KO mice and may play an anti-inflammatory role in IBD.

Dieulafoy Lesion: Successful Treatment of Massive Bleeding with Comhination Epinephrine Injection and Band Ligation. Z. Salem, MD, J. Fares, MD, H. Elfarra, MD, W. Baddoura, MD. St. Joseph's Regional Medical Center, Paterson, NJ, and Seton Hall University School of Graduate Medical Education, South Orange, NJ.

Introduction: Dieulafoy lesion is characterized histologically by an aberrant artery coursing beneath the mucosal surface. It can occur anywhere along the gastrointestinal tract with predominance to the proximal stomach. Its incidence as a cause of gastrointestinal bleeding varies between 0.3% and 6.7%. Endoscopic therapy has dramatically improved the management of these lesions. Multiple endoscopic modalities are reported to be effective. These include electrocoagulation, heater probe, injection sclerotherapy, laser photocoagulation, hemoclipping and band ligation.

Case Report: A 54 year-old man with history of hypertension, coronary artery disease, congestive heart failure, antiphospholipid syndrome, and mesangiocapillary nephritis with end-stage renal disease on hemodialysis was hospitalized with decompensated heart failure. His medications included warfarin, steroids and ASA. After responding to initial treatment, he developed a sudden episode of massive hematemesis and subsequently became hypotensive with systolic blood pressure of 60mmHg. Aggressive volume resuscitation was initiated. An emergent gastroscopy was performed which showed an actively spurting fundic vessel with normal surrounding mucosa, consistent with a Dieulafoy lesion. The bleeding site was injected with five mls of epinephrine 1/10,000 followed by band ligation. This provided immediate hemostasis and improved hemodynamics. Repeat endoscopy demonstrated a non-bleeding banded site and no additional pathology. A total of eight units of packed RBC's were required to bring the hemogram back to baseline. Patient remained stable throughout hospitalization with no further evidence of bleeding.

Conclusion: Early diagnosis and prompt endoscopic intervention is critical for successful management of Dieulafoy lesions. Combination therapy with epinephrine injection and band ligation may be an effective modality.

General Internal Medicine

Use of Metformin in the Medical Primary Care (MPC) Clinic at Elmhurst Hospital Center (EHC). A. Maslona, M.D., A. Lyman, M.D., MSCM Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Metformin has been shown in large randomized controlled trials to be effective in improving glycemic control in type 2 diabetic patients already treated with maximum doses of sulfonylurea agents (DeFronzo et al. Efficacy of metformin in patients with NIDDM. N Engl J Med 1995; 333:541–549). Since 1995, patients at MPC have been prescribed metformin in a similar strategy, yet data are lacking on the effectiveness of this approach in this particular patient population.

Methods: To evaluate the effectiveness of metformin used as an adjunct to sulfonylureas in MPC, we performed a quasi-experimental observational study of type 2 diabetics on maximum doses of glyburide for whom metformin prescriptions were approved by the EHC pharmacy between January 1998 and December 1999. Glycemic control (fasting plasma glucose [FPG] and hemoglobin A1c) was assessed before and after a stable maximum metformin dosage was reached. Secondary outcomes included body weight, fasting lipid levels, and side effects.

Results: During the study period, 110 patients received approval for metformin therapy: 56 patients (51%) met inclusion criteria and 54 (49%) were excluded, largely for lack of sufficient follow-up data. The average absolute improvement in FPG after metformin therapy was 73 mg% on an average daily dosage of 1908 mg of metformin. The average absolute improvement in hemoglobin A1c was 2.3%. The average follow-up period was 8.7 months. Univariate analyses showed that the degree of improvement was most closely related to baseline control; poor baseline control predicted enhanced response to metformin ($r = 0.600$, $p<0.001$). Improvement was less closely related to age, with increasing age predicting lesser improvement. Improvement was not related to ethnicity, gender, initial body mass index or change in BMI, history of a dietician visit, or the dose of metformin. Linear regression analyses showed that improvement in hgbA1c was significantly associated with baseline control and age (accounting for 43% of improvement, $p<0.001$). Metformin treatment had no effect on body weight, but had a marginally significant effect of lowering LDL cholesterol levels. No significant adverse effects were seen among the study patients.

Conclusions: Metformin is an effective way to improve glycemic control in type 2 diabetics already on maximum doses of sulfonylurea agents, especially among poorly controlled patients. It is safe in this setting, does not cause weight gain, and may have beneficial effects on lipid levels.

Evaluation of a Managed Care Curriculum in a Primary Care Internal Medicine Residency Program. L.M. Reich, MD, and R.A. David, MD. Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Background: In its 1998 Program Requirements for Residency Education in Internal Medicine, the ACGME included the recommendation that it is "desirable that each resident receive instruction in the principles of managed care." In order to adhere to the intent of this recommendation, as well as to ensure that our housestaff were adequately prepared to practice in the current medical environment, we developed a Managed Care (MC) curriculum, and integrated it into our Primary Care Internal Medicine Residency Program. One component of this curriculum was a monthly small-group discussion focussing on the practical issues involved in understanding MC. The purpose of the present study was to evaluate the success of this Workshop in terms of its utility to the housestaff and its effectiveness as a teaching modality.

Methods: All 36 residents in our Program as of June 2001 were asked to complete a survey designed to assess their educational experiences in the MC Workshop. They were asked to rank, on a 5-point Likert scale, their comfort level with the use, application, and discussion with patients of 13 concepts central to current MC issues, and to assess to what extent the MC Workshop improved or enhanced this level of comfort. They were then given 10 *true/false* questions designed to measure their understanding of key MC points. Their performance on this section was evaluated based on their individual experiences with the MC Workshop.

Results: Twenty-two of 36 house officers responded to the survey. Of these, 9 (6 interns and 3 junior and senior residents) never attended the MC Workshop, 8 attended a single Workshop, and 5 attended the Workshop more than once. The 13 house officers who attended the Workshop at least once included 6 senior residents and 7 interns and junior residents. The mean comfort level for all 13 MC topics increased from 2.79 before participation in the Workshop, to 3.51 after participation. The mean comfort level improved for 11 out of the 13 topics (only "Medicaid" and "Medicare" did not show this improvement). The performance on the 10-question test was clearly related to experience in the Workshop.

The mean percent correct score was lowest for those who did not attend the Workshop (60% for interns and 67% for residents), intermediate for those who attended once (78%), and highest for those who attended more than once (84%). Of those who attended at least once, senior residents did not outscore interns and junior residents (78% vs. 81%).

Conclusion: The inclusion of a MC curriculum as described above can be shown to increase Internal Medicine residents understanding of and comfort with important topics in Managed Care.

Screening for Risk Factors for Osteoporosis in Medical Primary Care Clinic (MPC) at Elmhurst Hospital Center. A. Sheikh, M.D., A. Lyman, M.D., MSCM Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Osteoporotic fractures in aging women are a major health problem in industrialized nations. In the United States, approximately 150,000 hip fractures occur annually in women over the age of 65. Epidemiologic studies have identified major risk factors; early screening for bone loss may allow detection before fracture occurs. A study was conducted at MPC to assess the prevalence of screening for osteoporosis.
Methods: A chart review was conducted of female patients without a prior diagnosis of osteoporosis in the clinic chart's Problem List who were seen at MPC for routine follow-up visits from February-March 2001. A convenience sample of patients scheduled for MPC appointments was selected. Clinic records were reviewed to ascertain documentation of a) daily calcium intake, smoking, alcohol consumption, exercise, family history; b) bone mineral density studies; c) treatment.
Results: Seventy charts were reviewed. Twenty-eight (40.6%) were aged 50-59, 30 (42.8%) were 60-69, 12 (17.1%) were 70-79. Fifty-two (74.3%) were Hispanic; Pakistani and East Asian origin each comprised 5 (7.1%), and Indian and African-American each comprised 4 (5.7%). Sixty-five patients (92.9%) had documentation of at least one screening question having been asked; smoking was assessed in all screened patients; 20 (28.6%) were questioned about daily exercise; daily calcium intake was documented for 4 patients (5.7%). Bone mineral density study was ordered in 14 (21.9%) and performed in 6 of these patients (42.9%). Sixty-three patients (90%) were prescribed calcium supplements; 19 (27.1%) were given hormone replacement therapy. Five patients had evidence in the chart of a diagnosis of osteoporosis; three (60%) received alendronate, one patient (20%) received calcitonin and 1(20%) was not treated.
Conclusions: Nearly all patients were asked at least one screening question, but excluding the assessment of smoking status substantially decreased the proportion screened. Only a fifth were referred for bone mineral density evaluation. Although calcium supplementation was used in 90% of patients, other preventive measures were uncommon. Further study is needed to assess strategies to increase primary and secondary prevention measures.

Utilization of Pulmonary Function Tests (PFT) in Medical Primary Care Clinic (MPC) at Elmhurst Hospital Center (EHC). R. Suleman, M.D., A. Lyman, M.D., MSCM. Primary Care Internal Medicine Residency Program. Elmhurst Hospital Center, Elmhurst, NY.

Aim: To evaluate the utilization of PFTs by primary care physicians at EHC.
Background: PFTs are utilized by primary care physicians in diagnosis, prognosis, treatment evaluation, and perioperative or disability assessment.[1]
Methods: A list of all patients referred from MPC from January–June, 2000 was obtained and a convenience sample of 50% was selected for review. Data were collected by chart review on demographic variables, pre-PFT diagnosis, indication for PFT, whether diagnosis was confirmed by PFT, whether change in clinical management resulted, and prognosis. Data were analyzed and graphs constructed using Excel software.
Results: One hundred sixty-eight patients were referred and underwent PFTs; 85 charts (50%) were reviewed. There were 36 males (42%); average age was 51 years; 32 (38%) were smokers. Frequency distribution by race/ethnicity: Hispanic—39 (46%), South Asian—20 (24%), white—12 (14%), East Asian—7 (8%), Black—7 (8%). Eighty per cent of patients were cooperative. Seventy-eight per cent of PFTs were ordered to confirm diagnosis. The pre-PFT clinical diagnoses were: asthma — 70 (82%), restrictive disease — 8 (10%), other [COPD, upper airway obstruction]— 7 (8%); 46 (54%) of PFT results were consistent with pre-PFT clinical diagnosis. Twenty-eight results (33%) were utilized to confirm diagnosis or appropriateness of therapy; 27 (32%) resulted in alteration of treatment plan and 2 (2%) were acknowledged but treatment was not altered. Nine (11%) of results were not acknowledged in the clinic chart notes. Eighteen (21%) of patients failed to return for follow-up. In summary, there were 79 PFTs (93%) that were definitely or possibly helpful in clinical management.
Conclusions: Results of this study suggest that PFTs are most likely to supplement the clinical management of outpatients with pulmonary disease if appropriately used. Further studies are needed to determine how utilization can be improved.

[1] Andrews JL. The clinical roles of PFT. Med Clin of NA 1979; 63:355–77.

Epidemiology of Hepatitis C at Elmhurst Hospital Center (EHC). K. Mostafizi, M.D., A. Lyman, M.D., MSCM. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Hepatitis C infection is the most common cause of chronic liver disease in the U.S., comprising 40–60% of cases and resulting in an estimated 8,000-10,000 deaths each year.

Although the number of newly acquired acute HCV infections has decreased from 180,000 in 1984 to 28,000 in 1995 in the U.S., immigration from countries with higher prevalence is occurring. A study was conducted at EHC, a public hospital serving a largely immigrant population, to determine the prevalence of infection among outpatients.
Methods: All patients who were enrolled in adult outpatient clinics and had a positive HCV antibody result (EIA) from 1999–2000 were identified from the data base of Infection Control. Demographic and clinical variables were extracted from the patient record and tabulated by hand. Univariate analyses were performed with EpiInfo software.
Results: The first 60 consecutive patients were selected from a total of 172 patients; ten charts (16%) were unavailable. Of the 50 patients included in the study, thirty-five (70%) were male. Race/ethnicity distribution was: African-American—15 (30%), Hispanic—15 (30%), Caucasian—10 (20%), other—10 (20%). Nineteen males (54%) and 7 females (47%) were injecting drug users [odds ratio (95% confidence interval) for males = 1.36 (0.34, 5.41)]. Four males (11%) and 0 females were hepatitis B surface antigen-positive [OR = undefined, p = .578]. Eight males (22%) and 2 females (13%) had serum transaminase levels > twice normal (results unavailable for 2 patients of each sex). Eight males (23%) and 0 females had cirrhosis [OR = undefined, p = .086]. Of the males, 8 (23%) were HIV+, 6 (17%) were HIV-, and 21 (60%) had no information in the chart; of the females, corresponding figures were 1 (7%), 3 (20%) and 11 (73%) [OR (95% confidence interval) of HIV-positivity for males = 4.95 (0.23, 235)]. Three males (8%) had an elevated (-fetoprotein level, 26 (74%) had a normal result, 6 (17%) were not tested; corresponding values for females were 0, 11 (73%), and 4 (26%). Thirty males (85%) had hepatic sonogram performed; 1 (3%) showed a mass lesion (expired before diagnosis). Nine females (60%) had a sonogram; all were normal.
Conclusions: In this population with a high proportion of substance abusers, better evaluation and follow-up may be indicated to ensure all patients requiring treatment receive it. A substantial proportion of patients were not evaluated for presence of hepatoma. No patients were undergoing interferon/ribavirin therapy. Utilization of a health educator may improve care of these patients.

Control of Hypertension in Elderly Type II Diabetics at Medical Primary Care Clinic at Elmhurst Hospital Center (MPC). S. Kats, M.D., A. Lyman, M.D., MSCM. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background. The incidence of diabetes is increasing in the United States as the population ages, and hypertension is twice as common in diabetics. JNC-VI recommends prompt pharmacologic therapy and lifestyle modification for the diabetic with even high-normal blood pressure (130–139/85–89 mm Hg). Microalbuminuria is a risk factor for both macrovascular damage and end-stage renal disease. Increased urinary microalbumin excretion is better correlated with systemic blood pressure than with many other variables; e.g., glycemic control, age, duration of diabetes, gender and body mass index. Therefore, a study was conducted to determine blood pressure control in diabetic patients treated in MPC.
Methods. A convenience sample of 100 patients seen within one week with dual diagnosis of hypertension and Type II diabetes mellitus was selected. Patients were included if they were aged 65 and older and had been under MPC care for more than 2 years. Electronic charts were reviewed. Mean blood pressure at the previous three visits, age, gender, ethnicity, treatment of hypertension and metabolic parameters (urinary microalbumin excretion, glycemic control, cholesterol and body mass index) were ascertained.
Results. Of the 100 patients included in the study, 41% were women and 53% were of Hispanic origin. The average age of the subjects was 72; 27% were overweight and 23% were obese. Ninety-eight per cent of subjects received pharmacologic treatment of hypertension, of whom 76% were on combination therapy and 74% were on ACE-inhibitors. Mean systolic blood pressure was 146.1 mmHg and mean diastolic blood pressure was 75.3 mmHg; mean glycosylated hemoglobin was 7.3. Nineteen per cent of the participants had blood pressure less than 130/80 mmHg (however, many subjects had isolated systolic hypertension with adequate control). There was no appreciable difference in blood pressure according to gender, race or age. Data on microalbuminuria were available for 26 subjects (28%), of whom 30% had urinary albumin excretion greater than 20 mg/L. Twelve patients (13%) had clinical proteinuria.
Conclusion. Blood pressure control in elderly diabetic patients at MPC is in accordance with JNC-VI guidelines. More aggressive screening for microalbuminuria is recommended. Further study is needed to identify strategies to maximize control of hypertension in these patients.

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The Diagnostic Value of Bronchoalveolar Lavage (BAL) in Sputum Smear-Negative Pulmonary Tuberculosis. E. Chang, M.D., M. Venkataraman, M.D., A. Lyman, M.D., MSCM. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: BAL is proven useful and widely used in the diagnosis of opportunistic infections, such as *Pneumocystis carinii*, in immunosuppressed patients with pulmonary infiltrates. However, its role in the diagnosis of sputum smear-negative pulmonary tuberculosis is less well established.
Methods: We conducted a cross-sectional study of all patients at Elmhurst Hospital Center from 1994 – 2000 who were diagnosed with pulmonary tuberculosis by either 1) positive *Mycobacterium tuberculosis* culture, 2) caseating granuloma(s) on histologic specimen or 3) clinical and radiological improvement following antitubercular therapy, who had undergone bronschoscopy and BAL and had had at least three consecutive AFB smear-negative sputum samples. Hospital records were reviewed for demographic and clinical data, and results were tabulated with Excel software.
Results: Thirty patients met inclusion criteria; 22 charts (73%) were available for review. Sputum cultures were positive for *Mycobacterium tuberculosis* in 17 (77%), compared to BAL cultures, which were positive in 13 (59%). All 5 sputum culture-negative patients were also negative on BAL culture. Four patients (18%) had positive BAL smears; all of these were ultimately sputum culture-positive. No diagnosis was made solely by BAL smear results; however, diagnosis was made sooner in these 4 patients. In addition, 4 patients (18%) underwent transbronchial biopsy; one (25%) had a positive smear of the specimen. This patient had negative smear and culture of both sputum and BAL specimens.
Conclusions: The diagnosis of pulmonary tuberculosis can be made in majority of patients from sputum culture alone. BAL resulted in a more rapid diagnosis in a small percentage (18%). We conclude that BAL should not be the only procedure used when bronchoscopy is performed. If rapid diagnosis is clinically important, efforts should be made to include transbronchial biopsy and polymerase chain reaction analysis, which have been shown in other studies to be helpful to increase diagnostic yield.

Colonoscopy Findings in the Elderly at Elmhurst Hospital Center (EHC). S. Caro, MD, A. Lyman, MD, MSCM; T. Riley, MD, A. Sharma, MD, and V. Gumaste, MD. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: Utilizing colonoscopy, the best methodology for colonic imaging, benign or malignant pathology is frequently encountered in the elderly population. The incidence of colorectal cancer (CRC) is positively correlated with age and generally occurs in individuals ≥ 50 years. The purpose of this study was to assess the indications and findings of colonoscopies in an elderly, multiethnic population conducted at EHC.
Methods: From the endoscopy suite database, a list of all colonscopies performed from 7/1/98 – 1/2001 was obtained and a convenience sample of consecutive eligible patients ≥ 60 years old was selected. Endoscopy suite charts and computerized records were reviewed, and age, sex, indication for the study, colonoscopic findings and pathologic findings were extracted. Indications were categorized as 1) bleeding (hematochezia, unexplained iron deficiency anemia, guaiac-positive stool), 2) symptoms (abdominal pain, diarrhea, constipation), 3) surveillance colonoscopy after a previous abnormality, and 4) weight loss.
Results: The first 75 eligible patients were selected. Age: 60-86 (mean = 69). Forty-four percent were male. The most common indication for colonoscopy was GI bleeding (47%), followed by surveillance colonoscopy (23%), GI symptoms (11%), weight loss (4%) and other (3%). The most common colonoscopy finding was hemorrhoids (66%), followed by polyps (31%), diverticuli (27%), cancer (9%), arteriovenous malformations (1%). CRC was found in 7 patients (9%); 6 (86%) were male [odds ratio (95% confidence interval) = 9.11 (.99, 429.04)]. Six (86%) with CRC had GI bleeding as the indication. Three (43%) of the cancers were in the rectum, 3 (43%) — sigmoid colon, and 1 (14%) — ascending colon. Of 29 polyps found (in 22 patients), location was: 14 (48%) — sigmoid colon, 6 (21%) each were in the ascending colon and descending colon, 3 (10%) - cecum, and 2 (7%) — rectum. None of the colonoscopies were completely normal in this study population. There were no complications.
Conclusions: The most common indication for a colonoscopy was GI bleeding and the most common colonoscopy finding was hemorrhoids. CRC was found in 9% of the patients; the proportion of cancers in the rectum was higher than expected. Males comprised 86% of the patients with CRC, consistent with the known higher rate of CRC in men. The low complication rate and high frequency of abnormal findings in this population support the use of colonoscopy for elderly patients with appropriate indications.

Profile of Elmhurst Hospital Center (EHC) Dialysis Patients (1965–1999). V. Kagramanov, MD; A. Lyman, MD, MSCM; and M. Neff, MD. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

End-stage renal disease (ESRD) is a serious medical, economic and public health problem in the US costing $16.7 billion/year in 1998 with projected costs rising to $28.3 billion by 2010 (1). EHC, a regional referral center for renal dialysis, was one of the first centers in the US, operating since 1965. A review was undertaken of EHC dialysis database, containing demographic and clinical data on all dialysis patients treated at EHC from 01/01/65 – 12/31/99, to describe trends in incident dialysis cases at EHC and to characterize EHC patients by demographic and clinical characteristics and indications for dialysis. A comparative analysis of contemporary EHC incident renal dialysis patients with corresponding data from US Renal Data System (USRDS) (2) (data available starting 1990) was undertaken to identify prevention strategies for ESRD in Queens County, NY. Data lacking personal identifiers were extracted from patient records. From 1965-1999, 2805 patients were treated in EHC dialysis center: 932 (32.2%) non-Hispanic whites (NHW), 1219 (43.5%) Blacks (BL), 439 (17.6%) Hispanics (HIS) and 161 (5.7%) Asian/Pacific Islanders (API). Nearly all patients (85.5 – 94.5%) were Queens residents. The proportion of BL among incident dialysis patients steadily rose from 28.5% (1965 – 69) to 55.4% (1990 – 94). HIS comprise the third most populous group among EHC incident dialysis patients (ranged from 12.3 to 20.7% (1995 – 99).

API increased (2.3% in 1970 – 74 and 9.4% in 1995 – 99). NHW tended to be older than other groups. Number of males> females, especially in NHW (61.6% males) and HIS (59.6% males) vs. BL (52.7% males); except for BL females >50 years. Diabetes (31%), hypertension (22%) and glomerulonephritides (24.7%) were the most frequent indications for dialysis at EHC. Diabetes was more frequent indication (42.2%-EHC vs. 34.1%-USRDS) probably due to higher proportions of BL and HIS in Queens County. BL dialysis patients are also more likely to have hypertension-, IVDU- and HIV-related ESRD. In API, HIS and NHW, glomerulonephritis (all types) is indication in incident cases in 35.8%, 33.5% and 24.7%, respectively. From 1990 – 2000, the population of Queens increased by 225,000 (11%); ethnic minorities, who have higher rates of ESRD, now comprise 71%. In view of these developments, EHC should expect to manage an increasing number of ESRD cases in the next decade.

1 Collins AJ. End-stage renal disease. Postgraduate Med 2000; 108(1):13 – 15.
2 2000 Annual Data Report of the U.S. Renal Data System. Am J Kidney Dis 2000; 36(6):15 – 36.

Highly Active Antiretroviral Therapy (HAART) at Elmhurst Hospital Center (EHC) Part II. M. Ciobatea, M.D. and A. Lyman, M.D. MSCM. Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: HAART significantly reduces morbidity and mortality in HIV patients. Plasma viral load appears to be the best predictor of long-term clinical outcome. Numerous randomized controlled trials have assessed the effect of HAART on viral load[1,2]. A study at Johns Hopkins Hospital showed that only 37% of patients receiving HAART had undetectable HIV-RNA 1 levels one year after initiation; main risk factors for failure were frequently missed appointments, young age and nonwhite race. A study conducted at EHC from 7/97 – 6/98[3] found higher rates of failure in males, Blacks, those aged 35 – 44, those missing > 10% of appointments, or those with ≤12 years of education. This study was continued to further examine the relationship of demographic and clinical factors on the viral load.
Methods: Retrospective cohort study utilizing chart review of all new medication-naive patients placed on a regimen containing protease inhibitors (PI) or non-nucleotide reverse transcriptase inhibitors (NNRTI) from January 1999 to December 2000. Age, sex, marital status, level of education, race/ethnicity, language spoken, and HIV risk factors [intravenous drug user (IVDU), homosexual/bisexual not IVDU, and heterosexual not IVDU] were abstracted from the medical records. Kept appointments (≥50% vs less) was obtained as an indirect indicator of adherence to treatment. Mean and median of all viral loads (VL) obtained at least one month after starting treatment. Results were tabulated and analyzed by hand.
Results: 211 patients were identified; 69 (32.7%) met inclusion criteria; 142 subjects (67.3%) were excluded. Mean VL was highest for those aged 35 – 44 (27442). Females had better response (953 vs. 12834). People with ≥12-grade education had lower VL (6248) than people who had < 12-grade (27529). Race/ethnicity: lowest for Caucasians (702) and highest for African-Americans (19677), single subjects had highest results (11401).

Unlike prior study, sample of IVDU was too small to permit reliable estimate of viral load. Heterosexuals (largest category) had the highest results (11812). Spanish-only-speaking had lower results than English-speaking (1593 vs.8218). Median VL was not appreciably different between various groups; the most frequent value was undetectable. Adherence to clinic appointments was lower for Caucasians and single patients, but showed no appreciable difference according to all other variables.

Conclusions: Mean VL was lowest for patients aged 18–24, females, education ≥ 12 years, Caucasian, widowed, and IVDU as risk factor; median VL were usually in the undetectable range. Adherence to clinic appointments was generally good, as measured by $\geq 50\%$ compliance. Adherence was lower for Caucasians and single subjects. Further studies on a larger sample, permitting meaningful subgroup analyses are indicated.

[1] Geghardt M, Rickenbach M, Egger M, and the Swiss HIV cohort study. Impact of antiretroviral combination therapies on AIDS surveillance reports in Switzerland. AIDS 1998; 12:1195–1201.

[2] Lucas G, Chiasson R, Moore R. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. Ann Intern Med 1999; 131:81–87.

[3] Marin M, Lyman A. Antiretroviral therapy in Elmhurst Hospital Center (EHC) HIV Clinic: Risk factors for virologic failure. Program and abstracts. Eighteenth Annual Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine Research Day.

Effect of Severity of Withdrawal Symptoms on Smoking Cessation in Subjects Treated with Clonidine or Placebo. A. Lyman, M.D., M.S.C.M.[1] and L. Covey, Ph.D[2].

Background: Nicotine withdrawal symptoms may increase risk of failure to quit or of relapse. An analysis was preformed on data from a double-blind placebo-controlled randomized trial of clonidine treatment of nicotine dependence[3] to determine if severity of withdrawal symptomatology was associated with failure to quit.
Methods: The study has been previously described. Exclusion criteria included major depression (MD) in past six months or antidepressant therapy in past six weeks. SCID and Fagerström Tolerance Questionnaire (FTQ) were administered to evaluate, respectively, history of MD and nicotine dependence. Withdrawal symptoms (craving, irritability, anxiety, depressed mood, restlessness, increased appetite, sleep disturbance, difficulty concentrating) were ascertained by self-rating on a six-point Likert scale one week post-quit date and summed to yield a total withdrawal symptom score (TWSS). Abstinence was assessed at the ten-week visit with confirmation by plasma cotinine. Logistic regression was performed to estimate the odds ratio of cessation for each five point increase in TWSS, using SPSS software.
Results: More than 85% of the sample was Caucasian and of middle or upper income; mean age = 45 years; median daily consumption = 30 cigarettes; mean duration of smoking = 28 years; nearly 80% had high scores on FTQ. Mean TWSS was 16.18 (maximum = 40). In a logistic regression model, only FTQ was significantly associated with cessation [odds ratio (95% confidence interval) = .851 (.735, .986)], TWSS, clonidine, and history of MD were not. Every one-point increase in FTQ score was significantly associated with a 15% decrease in the odds of cessation. A subject on placebo without history of MD with a high TWSS and high FTQ had a predicted probability (95% confidence interval) of cessation of only 18.77 % (17.20, 42.11), as compared to 50.53 (39.51, 61.49) for a similar subject with low TWSS and low FTQ.
Conclusions: Withdrawal symptom severity was not significantly associated with cessation in a clinical trial of clonidine (hypothesized to relieve withdrawal symptoms). Failure to identify significant predictors of cessation underscores need for further research to determine which, if any, symptoms are associated with failure or relapse, and to identify pharmacologic and behavioral means to address them.

[1] Primary Care Internal Medicine Residency Program, Mount Sinai Services at Elmhurst Hospital Center

[2] Dept. of Clinical Psychopharmacology, NYS Psychiatric Institute

[3] Glassman AH, Covey LS, Dalack GW, et al. Smoking cessation, clonidine, and vulnerability to nicotine among dependent smokers. Clin Pharmacol Ther 1993; 54:670–9.

Geriatrics

Interns Learning to Care for Dying Patients. Jennifer Rhodes-Kropf, M.D., Mount Sinai Geriatric Department, New York, NY; R. Adelman, M.D., Cornell Geriatric Department, New York, NY; and D. Meier, M.D., Mount Sinai Geriatric Department, New York, NY.

Objectives: To examine intern self-assessment of their care of dying patients. To examine intern assessment of the educational role of attending physicians in the care of dying patients.
Methods: The data was collected at a New York City Teaching Hospital. Interns were identified from death certificates of their patients during six months in the year 2000. Patient deaths were excluded if the deaths were unexpected or if the patients died in the intensive care unit. Intern interviews were scheduled within a few days after their patients' deaths. Fifty half hour structured interviews were completed by one interviewer. The questions were quantitative (Likert scale) and qualitative. The following topic areas were included; intern relationship with the dying patient, intern relationship with the dying patient's family, and intern relationship with the patient's attending physician.
Results: Fifty-eight percent of interns rated their comfort level in talking to their patient and family about end-of-life issues as good, 4 to 5 on the Likert scale of 1–5. Sixty percent of interns reported minimal emotional impact in terms of making their patient's experience with death emotionally easier, 1 to 2. Minimal time to spend at bedside was cited as the most important influential factor. Seventy-four percent of interns rated their patient's physical comfort level 4 to 5, 26% 1 to 3. Interns rated how well their patient's attending matched the definition of the ideal role model caring for a dying patient: 34% received a 1 to 3, 66% a 4 to 5. Observation of discussions by attendings with patients and families was rated as the most effective method to learn how to care for dying patients (mean 4.45 on the Likert scale).
Conclusions: The majority of interns are comfortable talking to their patients and families about end-of-life issues, but the majority also felt that they had minimal emotional impact. Interns think that observing attending interactions with patients is the most effective way to improve their skills caring for dying patients and their families, however, there is wide variability in attending performance in their capacity as role models caring for dying patients.

Hematology

Generation of Recombinant Adenoviruses for Gene Transfer of Anti-stathmin Ribozymes in Cancer Cells. Sucharita J. Mistry, Alex Bank, and George F. Atweh, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Stathmin plays an important role in the regulation of the mitotic spindle by promoting microtubule depolymerization. It is highly expressed in a wide variety of human cancers including leukemia, lymphoma, breast carcinoma, prostate carcinoma and ovarian carcinoma. We had previously shown that antisense inhibition of stathmin expression abrogates the malignant phenotype of leukemic cells *in vitro* and *in vivo*. We also showed that combination of antisense stathmin inhibition and drugs that target the mitotic spindle (e.g. Taxol) have synergistic antiproliferative effects. Ribozymes, which have the potential to catalytically cleave more than one molecule of the target RNA, may provide a more efficient approach for downregulating genes like stathmin that are expressed at very high levels in cancer cells. We had previously designed three novel hammerhead ribozymes that efficiently cleave native full length stathmin mRNA in a catalytic manner. We have now cloned two of these antistathmin ribozymes, Rz184 and Rz305, in a bicistronic adenoviral gene transfer vector (pQBI-AdCMV5-IRES-GFP) to coexpress antistathmin ribozyme and GFP. The potential growth inhibitory effects of the cloned antistathmin ribozymes were first analyzed in HeLa cells by a colony suppression assay. HeLa cells were cotransfected with the antistathmin recombinant vector and a neomycin resistance gene expression plasmid. In a control experiment, the cells were cotransfected with a neomycin resistance gene expression plasmid and a control ribozyme (RzC) carrying non-specific sequences that do not target stathmin. The G418 resistant colonies were counted after three weeks. HeLa cells that were cotransfected with pRz184.GFP and pRz305.GFP showed 77.3% and 90% inhibition of colony formation, respectively, compared to cells cotransfected with pRzC.GFP. This demonstrates that the antistathmin ribozymes are biologically active and have growth inhibitory effects *in vivo*. In order to achieve efficient gene transfer of anti-stathmin ribozymes in cancer cells *in vivo*, we generated a recombinant adenovirus construct expressing the antistathmin ribozyme. The adenoviral recombinants were identified by the presence of green fluorescent plaques and screened by PCR analysis. Out of 17 plaques, 8 showed the insertion of anti-stathmin ribozyme and GFP sequence into the Ad genome. We examined the antistathmin ribozyme activity of 5 of these clones by transducing 293 cells. After 48 hours of infection, nearly 100% of the cells were transduced as determined by the appearance of green fluorescence. Northern analyses of RNA isolated from the transduced cells showed 70–86% reduction in the level of stathmin mRNA relative to uninfected cells. This demonstrates that these recombinant adenoviruses are capable of efficient gene transfer of anti-stathmin ribozymes and can inhibit stathmin expression in transduced cells. The ability of these recombinant adenovirus to transduce different cancer cells is currently being investigated. These studies may lead to the development of a novel antistathmin ribozyme based therapeutic approach to cancer therapy.

A Novel Pathway for Activation of Hematopoiesis and Vasculogenesis in the Mouse Embryo. [1,2] M.A. Dyer, [2]D. Mohn, and [2]M.H. Baron. [1]Department of Genetics, Harvard Medical School, Boston, MA, and [2]Department of Medicine, Mount Sinai School of Medicine, New York, NY.

During mouse development, the first blood and endothelial cells arise from mesoderm induced and patterned by secreted signaling molecules. We demonstrated previously that specification of these lineages requires a signal(s) secreted from the adjacent visceral endoderm (VE) (Belaoussoff et al., 1998 Develop. 125:5009). Recently, we have reported (Dyer et al., 2001, Develop. 128:1717) that Indian hedgehog (Ihh) is a VE-secreted signal which alone is sufficient to induce formation of hematopoietic and endothelial cells. As seen with VE, Ihh can also respecify prospective neural ectoderm (anterior epiblast) along hematopoietic and endothelial (posterior) lineages. Downstream targets of the Hh signaling pathway (*Ptch1*, *Smo*, *Gli1*) are upregulated in anterior epiblasts cultured in the presence of Ihh protein, reflecting a response by the target tissue to the Hh signal. Dispersed cells from IHH-treated anterior epiblasts form primitive or definitive hematopoietic colonies in secondary cultures in the presence of appropriate cytokines, indicating that functional hematopoietic stem cells are produced. Blocking Ihh function in VE inhibits activation of hematopoiesis and vasculogenesis in the adjacent epiblast, suggesting that Ihh is an endogenous signal that plays a key role in the development of the earliest hemato-vascular system. We have shown that another family member, *Desert hedgehog (Dhh)*, is activated in the embryo during gastrulation and is expressed in the mature yolk sac mesoderm (Farrington et al., 1997, Mech. Dev. 62:197).

In *Ihh* null embryos, Dhh might compensate, at least in part, for the function of Ihh and may also stabilize the mesodermal patterning initiated by Ihh during early gastrulation. IHH-N upregulates expression of *Bmp4* in anterior epiblasts. Our recent work has demonstrated that recombinant human BMP4 protein can substitute for IHH-N in explant cultures. Therefore, the hedgehog signaling activities observed in our explant cultures might be mediated, in part, by Bmp4. Indeed, the BMP-binding protein noggin inhibits activation of hematopoiesis and vascular development in whole embryo explants as well as in HH-treated anterior epiblasts, indicating that Bmp signaling functions downstream from Ihh signaling in this pathway. Interestingly, *Hedgehog* genes and protein are expressed by adult mouse and human bone marrow stromal cells and *Ptch1* and *Smo* are expressed in hematopoietic stem/progenitor as well as endothelial cells. Recently it has been reported that, in postnatal mice, Sonic hedgehog can activate angiogenesis through upregulation of VEGF and angiopoietins. We suggest that Ihh and Dhh may also function in vascular development by regulating the expression not only of Bmp4 but also of vascular cytokines. Therefore, these findings may have important implications for regulating hematopoiesis and vascular development for therapeutic purposes in humans and for the development of new sources of stem cells for transplantation and gene therapy.
GCO#: 96-732ME and 98-425ME

Cross-Talk between Human Vascular Endothelial and Smooth Muscle Cells: An Explanation for the Atherogenicity of Lipoprotein(a). Nasreen Haque, Mark Taubman and Peter Harpel. Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Background: Monocyte/macrophage and vascular smooth muscle cells (VSMC) invasion of the intima is a hallmark of atherosclerosis. The lipoprotein Lp(a) is an independent risk factor for atherosclerosis but the mechanisms are not known. We have shown earlier that Lp(a) stimulates human vascular endothelial cells (HUVEC) to produce the CC chemokine I-309, a monocyte chemoattractant (Circulation. 2000;102:786–92). We have also reported that HUVEC express CCR8, the I-309 receptor, and that endothelial chemotaxis is induced by I-309 (Blood 2001; 97:39–45). We postulated that Lp(a) may induce monocyte chemotaxis into the vessel wall via stimulation of HUVEC I-309 and that this activity of Lp(a) may play a role in its atherogenicity. We now show that VSMC express CCR8 and transmigrate in response to I-309 and to Lp(a) stimulated HUVEC conditioned medium (LCM).
Methods and Results: We have found that I-309 and LCM induce VSMC chemotaxis and that this migration is inhibited by a monoclonal antibody we have produced against CCR8. Further, pertussis toxin inhibited VSMC migration in response to I-309 showing a Gi-coupled receptor response. Northern blot analysis of VSMC documented CCR8 mRNA. These results indicate that VSMC express functional CCR8. We have also found that I-309 stimulates VSMC to secrete metalloproteinase-2 (MMP-2) as assessed by gelatin zymography. MMP-2 activation appears critical for VSMC migration since neutralizing antibody to MMP-2, but not MMP-9, blocks both I-309 and LCM induced migration of VSMC through reconstituted basement membrane.
Conclusion: These results document that I-309 and I-309 induced in the CM of HUVEC by Lp(a), stimulate VSMC migration. I-309 also increases secretion of MMP-2 by VSMC, an activity that appears essential for I-309 induced VSMC migration through matrix. These new data support the concept that Lp(a) may induce molecular cross-talk between HUVEC and VSMC resulting in smooth muscle cell recruitment into the intima of the human atherosclerotic plaque.

New Generation of Retroviral β-globin Vector Capable of Transducing Hematopoietic Cells at High Level. Hassana Fathallah, H-Y. Lung, K. Chirkova, Y. Galperin, R.S. Weinberg, and G.F. Atweh.

One major obstacle to gene therapy of human sickle cell disease and β-thalassemia with retroviral vectors of the Moloney murine leukemia type is inefficient gene transfer into non-dividing hematopoietic stem cells. We have developed a new generation of HS-40 based retroviral vectors that carry a human beta (or gamma) globin gene as the therapeutic gene and the green fluorescent protein (GFP) gene as a selectable gene. The globin gene in these vectors is under the control of the human beta globin promoter while the GFP gene is under the phosphoglycerate kinase gene promoter. We demonstrate that these retroviruses are genetically stable in producer cell lines and can be produced at high titer. Following a three-day transduction protocol of murine bone marrow cells, gene integration in progenitor cells was determined by culturing cells in methylcellulose followed by a PCR assay for the presence of the viral sequences. Gene expression was analyzed in transduced cells by flow cytometry to determine the % of GFP positive cells. PCR analysis of individual colonies showed 60% of GFP and globin positive colonies while FACS analysis showed 16% of GFP positive cells. These retroviruses were also able to transduced peripheral blood cells from sickle cell patients at a reasonable efficiency (7% of GFP positive cells). High level of transduction and a selection based on GFP expression could potentially ensure the selection of transduced cells which express the transferred gene and eliminate nontransduced cells and transduced cells that don't express the transferred gene. Enrichment of transduced cells and their engraftment in the recipient bone marrow could make effective gene therapy of human beta-globin gene disorders an achievable goal.

Changes in Stathmin Expression during Megakaryocyte Maturation: A Potential Role In Endomitosis. Camelia Iancu and George F. Atweh, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Megakaryopoiesis is characterized by two independently regulated processes, functional maturation and polyploidization. In the process of polyploidization, immature megakaryocytes (megakaryoblasts) increase their DNA content to 2^x by a poorly understood process named endomitosis. Endomitotic cells are characterized by the presence of complex multipolar mitotic spindles, limited chromosome separation and absence of cytokinesis. The endomitotic cell cycle involves highly dynamic changes in microtubules that are essential components of the cytoskeleton and the mitotic spindle. Stathmin is a major cytosolic phosphoprotein that plays an important role in cell cycle progression by regulating the dynamics of microtubule polymerization and depolymerization both in interphase and mitosis. Inhibition of stathmin expression is associated with abnormalities in cell cycle progression, mitotic spindle formation and mitotic exit. We hypothesized that a regulation of the level of stathmin expression might be critically important for megakaryocyte differentiation and its loss of expression might be responsible for the abortive mitosis in megakaryocytes which is referred to as endomitosis. We first analyzed stathmin expression in two different human erythroleukemia cells cell lines (K562 and HEL cells) that are capable of both maturation and polyploidization following exposure to inducing agents. Upon exposure to phorbol ester or staurosporine stathmin mRNA expression was downregulated in a concentration and time dependent manner in both cell lines. This was associated with the appearance of a characteristic differentiated phenotype and upregulation of megakaryocytic specific markers. In addition, downregulation in stathmin mRNA expression correlated with increased DNA content of differentiated cells. We had previously found that partial stathmin inhibition in K562 cells increased the propensity of these cells to become polyploid upon exposure to staurosporine. Thus, these results in established cell lines strongly suggest that stathmin expression may also play an important role in megakaryocytic maturation of primary cells. Therefore, we derived primary megakaryocytes in culture from murine bone marrow to investigate stathmin expression during megakaryopoiesis. Immature and mature megakaryocytes were separated by density gradient separation. The different fractions were subsequently analyzed for the characteristic megakaryocytic morphology by light microscopy and for CD41 expression and DNA content by flow cytometry. We used a semiquantitative RT-PCR assay to determine stathmin mRNA expression at different stages of megakaryocyte maturation. Megakaryocyte progenitors with low ploidy levels (i.e. 2 to 4N DNA content) showed significant levels of stathmin mRNA expression. In contrast, mature megakaryocytes had no detectable levels of stathmin mRNA. More importantly, the absence of stathmin mRNA expression in these cells correlated with a high level of ploidy (up to 128N DNA content). Thus, these results support the hypothesis that the loss of stathmin expression might be associated with or even responsible for megakaryocyte polyploidization. Our findings are the first evidence for a potential involvement of stathmin in primary megakaryocyte maturation. Further investigations are underway to determine the role of stathmin expression during megakaryopoiesis *in vivo*.

Molecular Mechanism of Action of the BTB Class of Transcriptional Repressors. A. Melnick[1], F. Ahmad[2], V. Bardwell[3], G.G. Prive[2], and J.D. Licht[1]. [1]Derald Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY; [2]Department of Medical Biophysics, University of Toronto, Canada; and [3]Department of Genetics Cell Biology and Development, University of Minnesota.

The PLZF transcriptional repressor causes a refractory form of acute promyelocytic leukemia when fused to the retinoic acid receptor alpha. Its highly conserved N-terminal BTB domain plays a critical role in this disease since it is believed to recruit co-repressors that inappropriately silence target genes. The crystal structure of the PLZF BTB domain revealed an obligate homodimer with a highly conserved charged pocket formed by apposition of the two monomers. An extensive structure-function analysis showed that the charged pocket motif plays a major role in transcriptional repression mediated by PLZF. In the current study we wished to determine the mechanism of action of the BTB pocket in transcriptional repression. We found that mutations which neutralize key charged pocket residues without disrupting dimerization abrogated the ability of PLZF to repress transcription. Interestingly, loss of repression correlated with loss of interaction with N-CoR, SMRT and HDACs. We extended these structure function studies to the Bcl-6 protein, which is linked to the pathogenesis of non-Hodgkin's lymphomas. In this case, neutralizing the charged pocket also resulted in loss of repression and loss of co-repressor binding. We identified the BTB binding region of co-repressors and show for the first time a direct interaction between co-repressors, PLZF and Bcl-6. Further-more, a comparison of the PLZF, Bcl-6 and the FAZF^{ROG} protein shows that variations in the pocket results in differential affinity for co-repressors which predicts the potency of transcriptional repression. Thus, the BTB pocket is a novel molecular mechanism for recruitment of transcriptional repression complexes to target promoters.

Construction, Characterization, and Expression Analysis of Lentiviral Vectors That Carry the Human Beta and Gamma Globin Genes. Abdallah Nihrane and George Atweh. Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Retroviral-based transfer of a functional human globin gene and its integration in the genome of hematopoietic stem cells could provide a cure for Sickle Cell disease. Earlier generations of retroviral globin gene transfer vectors suffered from genetic instability, low titers and low levels of expression of globin genes in transduced cells. HIV- or FIV-based Lentivral vectors can be produced by transient transfections of three constructs (packaging construct, envelope construct and transfer vector) into 293T human kidney cells. The resulting lentiviral vectors are capable of infection, integration and stable expression in non-dividing target cells such as hematopoietic stem cells, hepatocytes, neurons and retinal cells. We have generated several HIV-based lentiviral vectors that express human globin genes under the enhancing activity of HS-40 element. The first vector carries the human beta-globin gene driven by its own promoter and modified by deleting recombinogenic IVS-2 sequence. The second vector carries a human gamma globin gene under the control of the beta-globin promoter. Lentiviral particles were prepared from concentrated or non-concentrated supernatants recovered from transiently transfected 293T cells and used to transduce Mouse Erythroleukemia (MEL) cells. Human globin gene expression in transduced MEL cells was assessed by S1 nuclease assays. In the absence of selection, the level of human beta-globin gene expression was greater than 10% of the expression of a single endogenous murine beta-globin gene. This suggests that the lentiviral vectors are giving rise to efficient gene transfer and a relatively high level of expression of the transduced human beta-globin gene. The gamma globin vector also expressed well in MEL cells. Further analysis is being conducted to accurately assess the efficiency of globin gene transfer and the level of human globin expression relative to that of the murine endogenous globin gene. We also generated similar globin vectors that include the GFP reporter gene. This modification should allow for more accurate estimation of viral titers and tracking of transduced cells both *in vitro* and *in vivo*. In the case of FIV-based vectors, four constructs were generated. A first vector carries eGFP gene driven by the CMV promoter. Two vectors carry either human beta- or gamma-globin genes linked to HS-40 regulatory element. The two remaining vectors carry eGFP reporter gene, together with either human beta- or gamma-globin genes linked to HS-40 regulatory element. These vectors were characterized and are being analyzed for the efficiency of transduction and expression of human globin genes *in vitro* and *in vivo*.

Infectious Diseases

Follow-up of Inadvertent Occupational Exposure to Resistant Tuberculosis via a Computerized Record System. D.A. Finch*, J. Williams*, A. Roveal*. *Bronx Veterans Affairs Medical Center, Infectious Disease Section, Bronx, NY.

Introduction: On November 11, 1999 the infection control service was notified by the microbiology lab that a patient on the acute care ward had a positive AFB smear of the sputum. The patient was subsequently diagnosed with miliary tuberculosis involving the brain, lungs, spleen, liver and kidneys. At the request of the NYC Department of Health, a contact investigation was initiated for all potentially exposed health care workers on duty for three months prior to the positive smear.

Methods: Hospital contacts were identified using hospital duty rosters and via a computerized patient record system (CPRS). At the Bronx VAMC, health care providers use the CPRS to write electronic progress notes and orders. Providers are identified via unique electronic signatures. Electronic progress notes were reviewed in full to identify any contact that may not have been identified via duty rosters.

Results: Six of 164 potentially exposed health care workers were not on any duty roster file. Based on CPRS notes, 49 of 164 employees were determined to have had close contact with the patient. Baseline tuberculin skin testing (TST) and repeat TST at three months post-exposure were recommended for all those who were TST negative. Eleven had previously positive TST. Three did not comply with TST. One new conversion was identified at annual follow-up. No secondary cases of active TB were identified.

Discussion: We conclude that electronic patient record systems can assist in contact investigations through clear documentation of health care provider contacts.

HIV Genotype Reports without Evidence of Significant Resistance Mutations: Incidence and Physician Interpretation of Medication Adherence at a Veterans Affairs Medical Center. D.A. Finch, MD*, A. Shahidi, PhD*, S. Brown, MD*. *Bronx Veterans Affairs Medical Center, Infectious Disease Section, Bronx, NY.

Introduction: It has been previously reported that HIV wild-type virus can re-emerge when anti-retroviral therapy is interrupted (Deeks. *NEJM* 2001; 344(7): 472–80). A recent study of electronic surveillance of adherence to anti-retroviral therapy found that physicians misjudge the degree of adhrence in 41% of their patients (Patterson. *Ann Intern Med* 2000; 133: 21–30).

Methods: The results of HIV genotyping peformed at the Bronx Veterans Affairs Medical Center between May, 2000–May, 2001 were reviewed to determine the incidence of reports without evidence of significant resistance mutations. Physician interpretaion of these results as a measure of adherence was assessed by reviewing physician encounter notes documented in a computerized patient record system.

Results: The microbiology lab at the Bronx Veterans Affairs Medical Center has performed 181 HIV genotype tests in the past twelve months. Ten genotypes (5.5%) did not reveal any significant resistance mutations. Physician interpretations were unavailable for one of ten results. Four of ten of these patients were thought to be adherent at the time the test was drawn; four of the four patients were subsequently considered non-adherent. Five of ten patients were known to have interrupted therapy at the time genotype testing was performed.

Discussion: This study confirms that physicians are willing to accept the presence of wild-type HIV virus as evidence of treatment interruption. This implies that large studies of clinical and virologic failure to respond to HIV anti-retroviral therapy will find that some failures are due to treatment interruption rather than HIV resistance.

Integrating Hepatitis C Screening and Counseling into an Existing Infectious Disease Clinic. E. Recher, C.S.W-R, J. Saporito, C.S.W and, D.A. Finch, M.D. Bronx VA Medical Center, Infectious Disease Section, Bronx, NY.

Introduction: Hepatitis C virus (HCV) is recognized as serious national public health problem. Limited surveys of Hepatitis C infection in the VA system have shown that the prevalence may be as high as 20% of all veterans. In the period from October 1, 1995 to March 31, 2001, the Bronx VAMC tested 14,800 veterans for the HCV antibody, 3,650 (25%) tested HCV positive. As per VA policy, HCV antibody testing and post-test counseling is offered to all veterans with past or present risk factors for HCV infection. At the Bronx VAMC, integration of HCV counseling and treatment into the I.D. Clinic evolved out of the existing HIV practice model.

Methods: We applied a multidisciplinary team approach because of the similarities in psychological responses of HCV diagnosis and. HIV diagnosis. All Bronx VAMC primary care providers are reminded to screen their patients for high risk for HCV infection via a computerized reminder. HCV elisa positive patients are referred to a newly created viral hepatitis clinic. Additionally, HCV testing is offered to veterans requesting HIV testing by the HIV social workers. Social workers trained in HIV test counseling give the results of HIV and HCV tests to patients during the post-test counseling session. These social workers took on the additional task of providing comprehensive initial HCV counseling to newly referred patients before they were evaluated by the physician. Veterans are first seen by one of the clinical social workers for HIV and/or HCV counseling, which includes a bio-psycho-social assessment. Baseline lab work and HCV confirmatory testing is drawn at this visit. Veterans are referred for medical specialist evaluation and other programs, i.e. psychiatry, substance abuse, as needed. Additionally, a new Hepatitis C educational and peer support group, co-facilitated by a social worker and nurse practitioner was formed.

Results: In the period from September 8, 1999–March 31, 2001, 418 veterans received comprehensive counseling regarding Hepatitis C.

Discussion: Integration of HCV counseling into an existing HIV counseling model is a method to address patient's biopsychoscial needs and the evaluation and management of an emerging epidemic.

HIV-1 Envelope Is a Neutral Antagonist to CXCR4 in T-Cells and Does Not Induce Interactions with G-Proteins. R. Staudinger[*], X. Wang[‡] and J.C. Bandrés[‡]. Departments of Neurology[*] and Pathology[†], New York University School of Medicine; Department of Medicine, Mount Sinai School of Medicine[‡] and Bronx VA Medical Center, ID Section, Bronx, NY[‡]

Background. The chemokine receptor CXCR4 is the principal coreceptor for X4 (T-tropic) HIV-1. HIV-envelope (gp120) interacts first with surface CD4 and then with CXCR4, a G-protein coupled receptor (GPCR). We analyzed the biochemical interaction between gp120 and CXCR4 and compared it with the one between CXCR4 and natural ligand stromal derivative factor-1 (SDF-1).
Results. Interaction with G-proteins. By using membrane extracts from CXCR4-rich T-cell line CEM we found that SDF-1 stimulated $[^{35}S]$-GTP-gamma-S binding to 210%, over control. Also, SDF-1 (20 nM) stimulated GTPase activity to 205 ± 5%. Alternatively, gp120$_{LAI}$ (300 nM), combined to 300 nM of sCD4, did not affect $[^{35}S]$-GTPgamma-S binding to CEM membranes and left the basal level of GTPase unaltered. Still, gp120$_{LAI}$/sCD4 (300 nM) reduced SDF-1stimulation of $[^{35}S]$-GTPgammaS binding to CEM membranes to 120 ± 14%. GTPase stimulation by SDF-1 was reduced to 108 ± 10%. In conclusion, HIV-gp120 does not induce interaction between CXCR4 and G-protein, but antagonizes the agonist effect of SDF-1.

Gp120 binding to CXCR4. Scatchard analysis of the homologous competition curve showed a single binding site, K_D=71.6 ± 17.14 nM and B_{max}= 3.77 ± 0.55 pmol/mg. Binding of gp120 was neither regulated by guanine nucleotides, nor affected by divalent cations and was temperature independent.

The affinity of gp120 $_{LAI}$ for CXCR4 was 10 times lower than for CD4 (KD of 8.2 ± 0.3 nM). This suggests a substantial role for CD4 to facilitate binding of gp120 to CXCR4.

SDF-1 binding to CXCR4. Similar analysis revealed two binding sites of CXCR4 for SDF-1. 13–20% of binding sites were of high affinity (K_D = 0.48 ± 0.1 nM), and the remaining of lower affinity (K_D = 9.6 ± 2.1 nM). ^{125}I-SDF-1 binding was highly temperature dependent. Inclusion of GTPgamma-S converted the higher affinity-binding site to the lower affinity site. Scatchard analysis revealed a homogeneous receptor population, K_D 5.75 ± 2.3 nM and B_{max} 3.16 ± 0.1 pmol/mg.
In conclusion, gp120 acts as an antagonist to a GPCR and the interaction of CXCR4 with HIV-1 viral envelope and chemokine exhibits fundamental differences that might help us devise new therapeutical approaches.

Allosteric Regulation of CCR5 by Guanine Nucleotides and HIV-1 Envelope. R. Staudinger[*], X. Wang[†], and J.C. Bandrés[‡]. Departments of Neurology[*] and Pathology[†], New York University School of Medicine; Department of Medicine, Mount Sinai School of Medicine[‡] and Bronx VA Medical Center, ID Section, Bronx, NY[‡].

Background: The chemokine receptor CCR5 is the principal coreceptor for R5 (macrophage-tropic) strains of HIV-1. Chemokine receptors belong to the super-family of GTP-binding protein coupled receptors (GPCR). Here, we report the biochemical consequences of the interaction between CCR5 and G-proteins and how HIV-1 envelope affects this interaction.
Results: Binding studies using ^{125}I- macrophage inflammatory protein (MIP)-1beta and membrane extracts from HOS-CCR5 cells showed that MIP-1beta binding to CCR5 was potently and specifically inhibited by guanine nucleotides. GTP inhibited MIP-1beta binding with an IC50 of 115 nM. The effects of GTP on the equilibrium binding properties of MIP-1beta were determined by using pre-incubation with increasing concentrations of GTP. GTP caused a concentration-dependent decrease in the computed number of binding sites (B_{max}), but had no effect on the affinity of the residual receptor sites. This indicated that the molecular mechanism of this inhibitory effect was a dose-dependent reduction in MIP-1beta receptors. We did not observe the appearance of a low affinity state.

Studies with HIV-envelope. In the absence of sCD4 the R5 tropic gp120W61D had no effect on MIP-1beta binding, indicating that binding of HIV-1 viral envelope to CCR5 is absolutely dependent on CD4. In the presence of sCD4, 100 nM gp120$_{W61D}$ inhibited ^{125}I-MIP-1beta binding to CCR5 by 56 ± 9%. Equilibrium binding data revealed that 100 nM gp120-sCD4 decreases the affinity of CCR5 for MIP-1beta (K_D = 425 ± 72 pM) with only a slight decrease in receptor density (B_{max} 1.08 ± 0.21 pmol/mg). Gp120-sCD4 had mostly a K_D effect on MIP-1beta binding to CCR5, so we examined this effect using kinetic studies. Gp120$_{W61D}$-sCD4 accelerated the decay of the MIP-1beta-CCR5 complex, indicating that gp120$_{W61D}$-CD4 is not a competitive ligand for the MIP-1beta binding site. Gp120$_{W61D}$-sCD4 also decelerated the association reaction of MIP-1beta to CCR5. The dissociation constants were as follows: 112 pM in the absence and 340 pM in the presence of 100 nM gp120$_{W61D}$-sCD4. All of this proves that HIV-1 envelope glycoprotein decreases the affinity of CCR5 for MIP-1beta, but also alters the kinetics of MIP-1beta binding to CCR5, indicating that it interacts with a distinct, but allosterically-coupled binding site.

Once Daily Dosing of Aminoglycosides (ODA) at the Bronx VA Medical Center. B.Ojofeitimi, D. Finch, and H.Fung. Bronx Veteran Affairs Medical Center, Bronx, NY.

The Aminoglycosides continue to be the mainstay therapy for the treatment of severe enterococcal and gram negative infections even though newer, less toxic antibiotics have gained FDA approval for clinical use. Aminoglycosides are usually used in combination with beta-lactams to provide synergistic effects although it can be used as a single entity for clinical conditions such as urinary tract infections. Studies have shown that pharmacodynamic, administrative and cost benefits do exist with the use of aminoglycosides once daily compared to multiple times daily. However, there are exceptions to the use of once daily dosing of aminoglycoside especially in certain patient populations and disease states, therefore its use should be carefully evaluated. This review will evaluate the use of once daily aminoglycoside dosing in our patient population with emphasis on side effects most importantly, changes in renal function.
Methods: Electronic charts of all patients who received once daily aminoglycoside dosing for the period 1998–2001 were reviewed retrospectively. Baseline renal function, gentamicin serum concentration and renal function parameters post aminoglycoside dosing will be analyzed.
Results: Only 5 patients (all male) were identified. Average age was 71 years. Three patients received ODA in Intensive Care Unit (ICU) and two in the medicine floor. All patients were on concomitant antibiotics including Zosyn, Kefzol and Flagyl. Only 1 patient was on Vancomycin, which could potentiate the nephrotoxic effect of aminoglycosides. Average duration of therapy was 7 days. Four patients had recently undergone surgical procedures (small bowel resection, aorticbifemoral bypass and tumor resection) complicated by infection or post-operative decompensation. One patient was treated for urosepsis.

Three patients (average age 80 years, average estimated creatinine clearance = 45 ml/min) with normal baseline renal parameters had an increase in BUN/Scr from baseline (50% increase serum creatinine).

Gentamicin trough concentrations in 3 patients were greater than 2 mcg/ml. Two patients (average age 57, average estimated creatinine clearance = 70 ml/min) had no change in renal function from baseline.
Conclusion: Once daily dosing of aminoglycosides is rarely used at our institution. The incidence of nephrotoxicity is high (3/5) probably due to decreased clearance of aminoglycosides in the elderly with impaired renal function.

Evaluation of a Safety IV Catheter (IVC) (Becton Dickinson, Insyte Autoguard): Final Report. *Meryl H. Mendelson, MD, B.Y. Lin-Chen, MPH, L. Finkelstein-Blond, RN, MA, E. Bailey, RN, MPH, G. Kogan, MS. Mount Sinai Medical Center and School of Medicine, New York, NY.

A safety IVC (BD, Insyte Autoguard) was evaluated at an 1,100 bed university affiliated medical center to determine efficacy in reducing needlestick injuries (NIs). NI rate during a baseline period I (non-safety; 6/93–8/96, 39 months) was compared to the study period II (2/99–7/00, 18 months). The study period included a two-month training (2–3/99) and a three-month pilot (4–6/99). Protectiv* Plus Catheter (Johnson and Johnson) was evaluated during the interim time between Period I and II. NI data was analyzed utilizing the CDC NaSH database. Two sharp disposal surveys were performed to assess usage and activation rates in 6/99 and 7/00; and two product evaluation surveys were conducted in 12/99 and 7/00. A 95% reduction in IV stylet related NIs was demonstrated comparing the baseline period I NI rate of 6.6/100,000 IV stylets (56 injuries/848,958 IV stylets) to the study period II NI rate of 0.3/100,000 IV stylets (1 injury/331,516 safety IV stylets) (p<0.001). The Period II NI occurred while the stylet was being withdrawn from the patient and the HCW failed to activate the safety mechanism. When comparing the two sharps disposal surveys, the 2nd survey activation rate was 91% vs. 85% (1st). The 2nd product evaluation showed 98% of HCWs answering the safety IV catheter was very easy/easy to use compared to 78% (1st). 95% (2nd) vs. 76% (1st) felt there was either no change/a slight change in technique needed to use this safety device. 99% of HCWs during both surveys answered the safety IV catheter provided effective protection against needlesticks. In conclusion, the Insyte Autoguard resulted in a marked and significant reduction in IV stylet-related injuries during the study period. Although this safety IVC requires activation by the user, the simplicity of the activation process promotes user compliance and therefore reduction in injuries. In that IV stylet-related injuries are high risk (hollow-bore needle, inserted directly into vein or artery), usage of this safety device should result in decreased blood-borne pathogen transmission to HCWs.
GCO#98-1046 ME*

Post C-Section Endometritis: Impact of Usage and Timing of Surgical Prophylaxis. M.H. Mendelson, MD, E. Santos-Cruz, BS, S. Gaddipati, MD, A. Adeyeye, RN, G. Kogan, MS, and J. Goldbold, PhD. Mount Sinai Medical Center and School of Medicine, New York, NY.

Prospective surveillance of post-partum endometritis following C-section (PPE) was performed to determine the role of antimicrobial prophylaxis and the impact of timing of prophylaxis for patients undergoing clean (not in labor with intact membranes prior to incision) and clean-contaminated (rupture of membranes, or intact membranes and in labor prior to incision) procedures. This surveillance was performed at the Mount Sinai Medical Center, a 1000 bed university affiliated hospital which performs approximately 5000 deliveries per year, 23% C-sections. From 8 – 10/99, there were 25 cases of PPE (CDC NNIS definition) following 286 C-sections (8.7%). The PPE rate was 4.0% for clean and 11.8% for clean-contaminated cases. When PPE rates were analyzed by prophylactic antibiotic usage and timing for clean cases: 0/25 (0)- pre-op (< 60 min prior to incision), 1/15 (6.6%)- intra-op(after cord clamping), and 3/59 (5.1%)- not meeting criteria (NMC) for pre or intra-op. For clean-contaminated cases PPE rates were: 3/35 (8.6%) pre-op, 6/35 (17.1%)-intra-op, and 9/83 (10.8%)-NMC. In conclusion, antibiotic prophylaxis when administered within 60 minutes prior to incision appears to be associated with a decrease in PPE following C-sections for both clean and clean-contaminated cases. Additional data is currently being collected to assess whether these findings will be statistically significant. If so, this data supports other analyses that have supported the effectiveness of antimicrobial prophylaxis for clean C-sections. Furthermore, the standard practice of administering antimicrobial prophylaxis after cord clamping will need to be re-evaluated.

Migraine Headaches during Treatment with Oral Ribavirin in Combination Therapy for Chronic Hepatitis. C. Norbert Bräu[1,2], Edmund J. Bini[3,4], Ayse Aytaman[5,6], Douglas A. Finch[1,2], Saray Stancic[7,8] Mount Sinai School of Medicine, Dept. of Medicine, I.D. Devision (1), Bronx VA Medical Center (2), NYU School of Medicine (3), VA New York Harbor HCS, Manhattan Campus (4), SUNY Downstate Health Science Center (5), VA New York Harbor HCS, Brooklyn Campus (6), New York Medical College (7), VA Hudson Valley HCS.

Background: Headaches have been associated with oral ribavirin (RBV) in early trials of RBV monotherapy for chronic hepatitis C. In treatment trials of RBV + interferon alfa-2b (IFN) for hepatitis C, headaches are described equally frequently in IFN monotherapy and in combination of IFN + RBV (63 – 68%). Specific links between migraine headaches and ribavirin therapy have not been reported to date.

Method: During May 1998 and December 2000, 452 patients were treated with IFN + RBV for chronic hepatitis C in four medical centers. All patients who developed new migraine headaches (confirmed by a neurologist) or had worsening of existing migraine during treatment were evaluated for a possible causal relationship with either IFN or RBV.

Result: A total of 9 of 452 patients (2.0%, 95% CI 1.1% to 3.7%) developed migraines during treatment with IFN 3 MU TIW + RBV 1000 – 1200 mg/d, 8 with a new diagnosis and 1 with worsening of existing migraine headaches. In 8 of 9 cases, a causal link with RBV treatment could be established: in 5 patients, migraine symptoms improved significantly when RBV dose was reduced or stopped and symptoms resumed with full RBV dose. In 3 patients there were no headaches with prior IFN monotherapy. In one patient, a temporal relationship with RBV was made because headaches occurred daily, even on days off IFN doses. All nine patients had severe migraine headaches that required opioid analgesics. In all 6 patients where the RBV dose was reduced, migraine symptoms became less severe. In 7 of 8 patients with new onset migraine headaches, the headaches resolved completely upon discontinuation of RBV. One patient with prior diagnosis of migraine ceased having severe headaches after RBV was discontinued and only had rare migraine attacks in a similar way as before RBV treatment. The one patient with a new diagnosis of migraine headaches who continued to have symptoms had had chronic headaches since adolescence, which in retrospect were judged by the neurologist as undiagnosed migraine-style headaches. Table 1 describes the nine patients.

Conclusion: Migraine headaches (usually new onset) may occur as a consequence of ribavirin therapy in about 2% of cases. They are typically severe and require opioid analgesics. Dose reduction of ribavirin therapy usually leads to improvement of migraine symptoms, and discontinuation leads to resolution in most cases.

TABLE 1

Characteristics of 9 Patients with Migraine Headaches on Ribavirin Treatment

No.	Age	Sex	HCV risk factor	Daily RBV dose [mg]	Migraine new/worse	Onset of migraine on RBV Rx	Link RBV migraine	Outcome of migraine after RBV D/C
1	43	M	IDU	1000	new	1 day	causal	continued
2	44	M	IDU	1200	worse	1 day	causal	mild, rare
3	37	M	IDU	1200	new	1 day	causal	resolved
4	46	M	IDU	1200	new	21 days	causal	resolved
5	51	M	IDU	1000	new	4.5 mo	causal	resolved
6	52	M	IDU	1200	new	4.0 mo	causal	resolved
7	40	M	Tattoo, cocaine, sex	1200	new	2.0 mo	temporal	resolved
8	40	M	IDU	1200	new	41 days	causal	resolved
9	45	M	IDU	1200	new	30 days	causal	resolved

Interferon Dose Increase for Early (Week 12) Non-Responders to Interferon Alfa-2b + Ribavirin Therapy for Chronic Hepatitis C Does Not Lead to a Viral Response at 48 Weeks. Norbert Bräu[1,2], Peiying Xiao[2], Douglas A. Finch[1,2], Charles S. Lieber[1,2] From the Mount Sinai School of Medicine, Dept. of Medicine (1) and Bronx VA Medical Center (2).

Background: At the end of treatment with interferon alfa-2b (IFN) and ribavirin (RBV) for chronic hepatitis C, the viral response rate (HCV RNA <100 copies/ml) is only 50%. Patients who have a poor response at treatment week 12 typically have a low treatment response. This study examined whether in such patients a dose increase of interferon can lead to a better outcome.

Methods: An open-label non-randomized parallel-group dose increase study was conducted in which patients with chronic hepatitis C (HCV RNA +) were begun on standard dose combination therapy (IFN 3MU TIW + RBV 1000 mg QD) for a total of 48 weeks. Patients were either treatment naive or had prior unsuccessful treatment with IFN monotherapy. Patients were considered early non-responders, if at treatment week 12 HCV RNA was reduced by less than 50% from baseline or ALT was elevated. These early non-responders were continued at treatment week 16 with an increased IFN dose of 5 MU TIW. Early responders were continued at the same IFN dose of 3 MU TIW. RBV dose remained unchanged in both groups. Primary endpoint was sustained viral response (SVR), i.e. HCV RNA < 100 copies/ml at post-treatment week 24. Secondary endpoints were viral response at end of treatment (EOT) and post-treatment week 48. Analysis was by intention-to-treat.

Results: Fifty-five patients were enrolled in the study, of whom 8 discontinued from the study before week 16. The remaining 47 patients continued at week 16 with an IFN dose of either 3 MU (n = 37) or 5 MU TIW (n = 11) and are used for this analysis. Both groups were similar in HCV genotype (1 = 87.5% 2 + 3 = 12.5%), baseline HCV viral load (median 3.4 M copies/ml), prior treatment vs. naive, and demographics. Among the 47 subjects, 3 were lost to follow-up and were considered end of treatment non-responders. One patient in the 5 MU group had HCV RNA <100 copies/ml at weeks 12, 48, 72, and 96 with abnormal ALT throughout due to Parkinson medication rather than hepatitis C. He was reclassified as early responder. The results of viral response and early discontinuation in each group are displayed in table 1. No early non-responder had a response to treatment with increased IFN dose of 5 MU TIW + RBV 1000 mg/d. By contrast, early responders had a significantly higher rate of EOT viral response of 35.1% ($p = 0.025$) and SVR of 29.7% ($p = 0.049$). All 11 sustained viral responders remained HCV RNA negative at follow-up week 48.

Conclusion: Increasing the IFN dose from 5MU TIW at week 16 for early non-responders to IFN 3 MU TIW + RBV 1000 mg/d does not lead to a viral response at the end of 48 weeks of treatment. It may lead to more treatment discontinuation due to side effects. A sustained viral response at follow-up week 24 remains sustained at week 48.

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TABLE 1

Viral response and early discontinuation

Treatment group	N	Viral response end Rx (EOT)	Viral resp. post-Rx wk 24 (SVR)	Viral resp. post-Rx wk 48	SVR genotype 1	SVR genotypes 2+3	Early D/C
Early responders	37	35.1%	29.7%	29.7%	21.9% (n = 32)	80.0% (n = 5)	16.2%
Early non-responders	10	0.0%	0.0%	0.0%	0.0%	0.0%	30.0%
p value (Fisher's exact test)		0.025	0.049	0.049	0.15	0.33	0.29

Liver Diseases

KLF6 Upregulates p21 Expression Through Recruitment of Histone Acetyltransferases CBP and PCAF. Dan Li[1], Steven Yeah[1], Goutham Narla[1], Francis J. Eng[1], Martin J. Walsh[2] and Scott Friedman[1]. [1] Division of Liver Diseases, Department of Medicine, [2] Division of Pediatrics, Mount Sinai School of Medicine, New York, NY.

KLF6 is a ubiquitously expressed "Kruppel-like" transcription factor whose mRNA is upregulated in a biphasic manner following partial hepatectomy. We have previously shown that KLF6 induces growth arrest in vivo by transcriptional upregulation of p21 independent of p53. Histone acetyltransferases (HATs) are chromatin-remodeling proteins critical for regulating gene transcription. Recent evidence suggested that acetylation of non-histone proteins by HATs play an important role in modulating the functions of these proteins, many of which are transcription factors. The **aims** of this study were to investigate whether KLF6 is a substrate for acetylation by histone acetyltransferases CBP and PCAF, and whether the acetylation of KLF6 is critical for its transcriptional upregulation of p21.
Methods: Chromatin-immunoprecipitation (ChIP) assay was performed to examine whether KLF6 physically binds to endogenous p21 promoter. Co-immunoprecipitation/Western analyses were carried out in 293T cells transfected with KLF6 and CBP, KLF6 and PCAF, respectively. Luciferase reporter assays were used to study whether CBP and PCAF synergize with KLF6 in transactivating p21.

In vitro HAT assays were performed to examine whether KLF6 can be acetylated by CBP and PCAF.
Results: ChIP assay revealed that KLF6 physically binds to the endogenous p21 promoter, confirming p21 as a direct target of KLF6. The physical interactions between KLF6 and both CBP and PCAF were demonstrated by co-immunoprecipitation/Western analysis. Co-transfection/luciferase reporter assays showed that CBP increases by 6-fold the transactivation of p21 promoter by KLF6, with 5-fold further increase when 100nM histone deacetylase (HDAC) inhibitor trichostatin A (TSA) was added. PCAF increased the KLF6's transactivating p21 by 10-fold, which was also further increased by the addition of TSA. *In vitro* HAT assays revealed that KLF6 can be heavily acetylated by CBP and modestly acetylated by PCAF. In order to determine acetylation of which lysine residue(s) may be important in p21 upregulation, 10 lysine to arginine point mutants were constructed and their abilities to transactivate endogenous p21 gene characterized. Western blots showed that K(74, 80)R, K124R, K280R have marked reduced ability to transactivate endogeneous p21 genes, suggesting the acetylation on these residues may be important for the upregulation of p21 by KLF6.
Conclusions: Our results demonstrated that KLF6 transactivates p21 gene through recruitment of histone acetyltransferases CBP and PCAF. KLF is a substrate for acetylation by both CBP and PCAF, and abolishing the acetylation on certain residues will markedly reduce KLF6's ability to transactivate p21, suggesting acetylation on these residues is important for the antiproliferative effets of KLF6. This provides new insights into the gene regulation during liver regeneration following parenchymal liver injuries.

Medical Oncology

Isolation and Characterization of Retroviral Particles from Human Breast Cancer. S.M. Melana[1], S. Dales[2], J. F. Holland1, B. G-T. Pogo[1], 1Division of Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; [2]The Rockefeller University, New York, NY.

We have previously reported sequences homologous to the *env* gene of the mouse mammary tumor virus (MMTV) but not to the human endogenous retrovirus K-10 in 38% of American women's breast cancers. The sequences were absent from other human tumors and tissues; they were expressed in most of the positive breast specimens. The complete 9.9 kb proviral structure of an MMTV-like agent has now been amplified and sequenced in two breast cancers. Structural features of this provirus indicate that it could be functional. The presence of viral particles and viral genes have now been investigated in primary cultures of *env* positive tumors.

When examined by electron microscopy, the cells show budding retroviral particles. Particulate fractions from culture media show reverse transcriptase (RT) activity, and the presence of viral genes as detected by RT-PCR. The RT activity peaked at densities characteristic of retroviruses in sucrose gradients. Furthermore, viral sequences have been detected in the particulate fractions. None of these properties were observed in similar studies with putatively normal breast cell lines. Taken together, these findings support the conclusion that a human mammary tumor virus, HMTV, similar to MMTV, has been identified. GCO#: 77-107

Effects of Ribozyme (Rz) Targeted against Deletion-Mutant (d) *EGFR* mRNA on Growth of Human Glioblastoma Multiforme (GBM) Tumor Implanted in Mice. C.F. Qu, M-E. Halatsch, J. F. Holland, T. Ohnuma. Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

In GBM, amplification of the *EGFR* gene is frequently present. Approximately half of the amplified genes are rearranged to delete a DNA fragment containing exons 2 to 7 (*EGFR*vIII). As a result of the (d), the fusion junction of the gene is created directly upstream of a Rz target codon (GUA). Previously, we have reported construction of a hairpin Rz directed against (d)*EGFR* mRNA (anti-(d)*EGFR*-Rz). When the specific Rz was transferred via a retroviral vector (N2A-(d)*EGFR*-Rz) into GBM cell line U-87MG which overexpressed (d)*EGFR* (U-87MG.(d)*EGFR*), the Rz was capable of specifically inhibiting (d)*EGFR* expression and was able to markedly reduce the clonogenic property of tumor cells in soft agar (J Neurosurg 2000; 92:297).
Aims: In the present study, we evaluated whether anti-(d)*EGFR*-Rz could render U-87MG.Δ*EGFR* cells less malignant *in vivo*.
Methods: U-87MG.Δ*EGFR* cells were infected with N2A-(d)*EGFR*-Rz and Rz-expressing cells were selected by limited dilution method (U-87MG.(d)*EGFR*-Rz). In culture medium containing 10% FBS, the cell growth rate of U-87MG.(d)*EGFR* and U-87MG.(d)*EGFR*-Rz was identical. 5×10^5 U-87MG.(d)*EGFR*-Rz cells were inoculated subcutaneously in male SCID mice and tumor appearance and tumor size were compared with those of U-87MG.(d)*EGFR*. In a therapeutic experiment, large amounts of N2A-(d)*EGFR*-Rz were produced by micro-ping-pong method (Bunnell and Morgan), cross-infecting amphotropic GP+*env*AM 12 packaging cells and ecotropic GP+E86 packaging cells alternatively, followed by centrifugation (final product 7×10^7 CFU/ml). For the Rz treatment of mice implanted s.c. with 5×10^5 U-87MG.(d)*EGFR* cells, the concentrated retrovirus-containing anti-(d)*EGFR*-Rz was injected at the implant site (MOI 30 CFU/cell/day) on days 2 – 8. Notation of the tumor appearance and measurement of tumor size was made.
Results: U-87MG.(d)*EGFR* tumor nodules appeared by day 10 and grew with a volume doubling time of 2 days; by day 20 the tumor size exceeded 1 cm^3. In contrast, when U-87MG.(d)*EGFR*-Rz cells were implanted, the appearance of a tumor nodule was delayed until day 19. Likewise, retroviral treatment with Rz resulted in similar delays in the appearance of U-87MG.(d)*EGFR* tumors.
Conclusion: Our observations show that the anti-(d)*EGFR*-Rz is capable of decreasing (d)*EGFR*-mediated high tumorigenicity in mice. This phenomenon was seen both after transduction of Rz *in vitro* or local injection of retrovirus expressing Rz at the U-87MG. (d)*EGFR* tumor implant site. The delayed tumor growth may be due to contamination with cells that had low or no expression of the Rz and/or expression of other oncogenes present in the parent U-87MG cells. GCO#: 77-107ME

Construction of a Multitargeted Multiribozyme System Targeted against Both *MDR*1 and *MRP*1, and its Cleavage Activity. D.P. Xu, T. Ohnuma, F-S. Wang, J.F. Holland, Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Previous work from our laboratory showed that stem II-modified hammerhead ribozymes (Rzs) targeted against the codon 196 of *MDR*1 mRNA (196*MDR*1-Rz) were able to completely reverse the multidrug resistance (MDR) phenotype of human lymphoma cells overexpressing P-glycoprotein (Human Gene Ther 1999; 10:1185). Combined overexpression of *MDR*1 and *MRP*1 has been reported in clinical tumor samples including AML cells, prostate and GI cancers. Simultaneous expression of *MDR*1 and *MRP*1 was shown to have a strong negative impact on response and survival of patients with AML.

Aims: We set out to develop a multitargeted multiribozyme system expressing both anti-196*MDR*1-Rz and anti-210*MRP*1-Rz.

Methods and Results: To construct this system, first we synthesized Rzs targeted against GUC sites of different codons of *MRP*1 mRNA. After having shown that a Rz targeted against the GUC site of codon 210 of *MRP*1 mRNA (210*MRP*1-Rz) had high cleavage activity, we designed a shotgun type multiribozyme structure containing 4 cis-Rzs and 2 potential trans-Rz cloning sites (Coat-Rz) with computer-assisted assessment of secondary structure. We initiated construction of an upstream half-Coat (Coat'A) containing two cis-Rz sequences, GUC cleavage sites and one trans-Rz cloning sites (BamHI, Xbl and SalI) through PCR elongation using synthetic oligonucleotides as template and primers. The Coat'A was inserted into a cloning vector pGEM3Zf(-) (Coat'A-pGEM). Previously constructed 196*MDR*1-Rz and 210*MRP*1-Rz were individually cloned into the Coat'A-pGEM (196Coat'A-pGEM and 210Coat'A-pGEM). The downstream half-Coat (Coat'B) was obtained from Coat'A-pGEM by PCR using primers containing HindIII ligation sites at the both ends. Empty Coat'B, Coat'B containing 210*MRP*1-Rz and 196*MDR*1-Rz were then individually ligated downsteam in tandem to create empty full Coat-pGEM, 196/210Coat-pGEM and 210/196Coat-pGEM, respectively. Orientation of downstream Rz was confirmed by DNA sequence analysis. After transcription, excellent self-cleavages with liberation of both 196*MDR*1-Rz and 210*MRP*1-Rz from Coat-Rz by cis-ribozymes were recognized after one hr at 37°C and 5mM Mg^{++} concentration. The *MDR*1 and *MRP*1 target gene fragments were obtained through RT-PCR using total RNA isolated from human laryngeal carcinoma KBv200 cells, which overexpressed both *MDR*1 and *MRP*1. The two ribozyme system expressing both 196*MDR*1-Rz and 210*MRP*1-Rz effectively cleaved *MDR*1 and *MRP*1 target mRNAs. Cleavage activity was not influenced whether the position of Rz was upstream or downstream in tandem structure and whether the Coat-Rz contained single or double trans-acting Rz(s).

Conclusion: We developed a double-functional double-ribozyme system targeted against *MRP*1 and *MRP*1 mRNAs. Adenovirus expressing this ribozyme system is being developed for transduction into target tumor cells. This versatile Coat-Rz system can be utilized for creation of multi-functional systems by adding tandem additional Rzs and for liberation of any other therapeutic genes (Rzs/antisense). GCO# 77-107ME

Effects of Transduction of Anti-MDR1-Ribozyme on Drug Sensitivity of Multidrug Resistant Human Lymphoma Growing in SCID Mice. LY Liu, T Ohnuma, DP Xu, CF Qu, FS Wang, JF Holland, Division of Medical Oncology, Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY.

We have previously reported that infection with Moloney murine leukemia-derived retrovirus N2A which expressed stem II modified hammerhead ribozyme (Rz) against GUC sequence at codon 196 of *MDR*1 mRNA (196*MDR*1-Rz) resulted in complete reversal of the multidrug-resistance (MDR) phenotype of P-glycoprotein-positive Daudi human Burkitt lymphoma cells, Daudi/MDR_{20} (Daudi cells which were 20-fold resistant to vincristine (VCR) *in vitro* (Hum Gene Ther 1999; 10:1185).

Aims: In the present study we have extended our *in vitro* observations to a mouse model using both Daudi/MDR_{20} cells previously transduced *in vitro*, and Daudi/MDR_{20} cells transduced in vivo after transplantation.

Methods: SCID mice were implanted i.v. with Daudi/MDR_{20}-196*MDR*1-Rz (196*MDR*1-Rz transduced Daudi/MDR_{20} cells) on day 1, and treated with VCR i.p. for 5 days (days 2–5). Survival was observed. Daudi/wt and Daudi/MDR_{20}-mut-196*MDR*1-sRz (Daudi/MDR_{20} cells transduced with 196*MDR*1-sRz in which stem II had been mutated and thus disabled) served as controls. In order to test therapeutic activity of the Rz, a recombinant adenovirus (Ad-5) expressing 196*MDR*1-Rz was developed through cotransfection of 196*MDR*1-Rz containing adenoviral vector pCA14 and rescue vector pJM17 into a packaging cell line (human embryonic kidney cell line 293). After 14–20 days the plaques formed were picked up and subcultured in new culture plates containing the packaging cells. When cytopathic effects were observed 3–5 days later, cells were frozen and thawed, and the supernatant containing Ad5 particles was harvested by centrifugation (Ad5-196*MDR*1-Rz).

After confirmation of the presence of Rz by PCR, virus was further amplified and purified by CsCl gradient centrifugation, followed by dialysis. The mice were implanted s.c. with Daudi/MDR_{20} and then treated immediately or 5, 12 or 19 days later with Ad5-196*MDR*1-Rz (MOI 400) x 3 days (days 1–3), followed by 5 days of i.p. VCR treatment (days 2–6). Time of tumor appearance was observed.

Results: VCR chemotherapy resulted in 80% of mice bearing Daudi/MDR_{20}-196MDR1-Rz cells (3 x 10^6 cells) with long-term survival (>120 days), exactly overlapping with that of wild-type Daudi cells treated with VCR. All the mice who were treated with PBS died in 19–25 days, as was true for VCR treated mice bearing Daudi/MDR_{20} cells or mutated Rz-transduced Daudi/MDR_{20} cells. For the therapeutic experiments, immediate administration of Ad5-196MDR1-Rz at the site of the Daudi/MDR_{20} implant resulted in increased VCR sensitivity manifested by approximately a 3-fold delay in tumor occurrence (day 77) as compared to virus untreated group or delayed virus injection groups (days 26–39).

Conclusion: Retrovirus-mediated transduction of anti-*MDR*1-Rz reversed chemoresistance of MDR human lymphoma cells when transplanted in mice. Likewise, immediate local injections of Ad5-196*MDR*1-Rz substantially decreased chemoresistance of mice bearing human MDR lymphoma cells.

With further improvements in *in vivo* transduction methodology, anti-*MDR*1-Rz may serve as an adjuvant in the chemotherapy of human MDR tumor. GCO#: 77-107ME

Orthopedics

Transforming Growth Factor Beta (TGF-β) in Synovial Fluid. B.M. Mehling, L.B. Keil, V.A. DeBari. Departments of Medicine and Orthopedics, St. Joseph's Regional Medical Center, Paterson, NJ.

Background: The transforming growth factors beta (TGF-β), TGF-β1 and TGF-β2, are believed to play a role in cell development relevant to wound healing. This not withstanding, there are few data on the issue of TGF-β in synovial fluid.

Purpose: The purpose of this study was to determine if detectable levels of TGF-β could be found in synovial fluid and if TGF-β existed free or as a pre-procytokine associated with latency-associated protein (LAP).

Methods: Patients undergoing knee surgery, both arthroscopic and open, consented (protocol approved by human subjects committee) to the donation of synovial fluid for analysis. Specimens were stored at −70°C until analyzed using an enzyme-linked immunosorbent assay (R & D Systems, Inc.) with TGF-β receptor as the capture protein and peroxidase-tagged anti-TGF-β as the probe. The activation procedure utilized HCl followed by neutralization.

Results: Negligible TGF-β was detected in synovial fluid in which the TGF-β was not activated. Levels of TGF-β in activated specimens were found to be 332 ± 382 pg/ml for TGF-β1 and 274 ± 203 pg/ml for TGF-β2. These were significantly higher ($p<0.0001$) than levels detected in the unactivated specimens.

Conclusions: TGF-β exists in synovial fluid as a pre-pro-growth factor and is detectable when LAP is cleaved. It is unclear at this point whether the levels of synovial fluid growth factors in healthy patients vary from those in patients with knee pathology.

Reproducibility of Bone Measurements by Dual Energy X-Ray Absorptiometry. Brett A. Sears, MPT; Ann M. Spungen, EdD; Roberta Modeste-Duncan, BA; Joanah C. Lessey; and William A. Bauman, MD.

Introduction: Bone mass is rapidly lost during the acute phase of spinal cord injury (SCI) and continues to be lost during the chronic phase at a rate that exceeds the average loss associated with aging in the able-bodied population. Dual energy x-ray absorbtiometry (DXA) is a method of measuring bone tissue mass and density.

Aim: The purpose of this study is to determine the reproducibility of total body and regional bone mineral content (BMC) and density (BMD) measurements using DXA in persons with SCI compared with that in able-bodied individuals. Design: A prospective, two-group, repeated measures study was performed.

Methods: DXA measurements (LUNAR DPX-IQ) were obtained in 15 individuals (5 female able bodied [AB], 4 male AB, and 6 males with chronic SCI) on 4 occasions within a 7-day period. BMC and BMD measurements were determined for the total body and regionally for the arms, legs and trunk.

Results: For total body BMC measurements, coefficients of variation ranged from 0.88 ± 0.40% in able-bodied males to 2.44 ± 1.74% in paraplegic males. Total body BMD measurements varied even less, from 0.63 ± 0.06% in paraplegic males to 0.90 ± 0.48% in able-bodied males. Regional bone measurements for BMC and BMD of the arm, leg, and trunk also had acceptable coefficients of variation. Coefficients of variation (%) for each group by region and total body are reported in the table.

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	Arm BMC	BMD	Leg BMC	BMD	Trunk BMC	BMD	Total BMC	BMD
AB Female (n = 5)	2.92 ± 1.26	0.88 ± 0.53	1.12 ± 0.51	1.08 ± 0.70	3.62 ± 2.17	1.48 ± 0.98	1.10 ± 0.63	0.78 ± 0.25
AB Male (n = 4)	1.50 ± 0.78	1.23 ± 1.01	1.18 ± 0.36	1.83 ± 0.91	2.48 ± 1.51	0.65 ± 0.24	0.88 ± 0.40	0.90 ± 0.48
Para Male (n = 3)	4.57 ± 4.14	2.03 ± 1.64	1.73 ± 0.61	1.43 ± 0.70	6.10 ± 2.65	2.70 ± 0.458	2.44 ± 1.74	0.63 ± 0.06
Tetra Male (n = 3)	1.73 ± 0.35	1.47 ± 0.23	1.33 ± 0.98	1.50 ± 1.22	37 ± 1.05	0.90 ± 0.27	1.90 ± 1.32	0.80 ± 0.36

Conclusion: BMD and BMC measurements obtained by DXA are highly reproducible in able-bodied and SCI individuals. Thus. regardless of the degree of osteoporosis and dramatic soft tissue compositional changes in persons with SCI. DXA remains a highly reproducible means to assess bone mass.

Pulmonary

Estrogen Receptors Alpha and Beta Expression and the Effects of Estrogen and Tamoxifen in Human Lung Cancer Cell Lines. C. F. Caracta[1]. C.A. Powell[2]. L. Wei[3]. J. S. Brody[3]. Q. Yu[1] [1]Mount Sinai School of Medicine. Department of Medicine. Division of Pulmonary and Critical Care. New York. NY: [2]College of Physicians and Surgeons. Columbia University. Division of Pulmonary. Allergy. and Critical Care Medicine. New York. NY: and [3]Boston University School of Medicine. The Pulmonary Center. Department of Pulmonary and Critical Care. MA.

Epidemiologic and experimental evidence suggest that sex hormones may play a role in the incidence and progression of lung cancer. We surveyed. by RT-PCR and sequencing. twenty-three human lung cancer cell lines for expression of estrogen receptors: Estrogen alpha receptor (ER alpha) and estrogen receptor beta (ER beta) and its isoforms. Seven of the nine adenocarcinomas (78%) expressed ER alpha. vs. three of fourteen (23%) other cell types ($p<0.03$). Adenocarcinomas tended to express both receptors vs. other cell types (55% vs. 23%). To study functional consequences of ER expression. we assayed in low serum. hormone-free media. cell proliferation by BrdU incorporation and apoptosis with a propidium iodide assay in response to various concentrations of estradiol and tamoxifen. using MCF-7 breast cancer cell lines as a positive control. MCF-7 increased proliferation in response to estradiol and tamoxifen induced MCF-7 apoptosis that was blocked by addition of estradiol. None of the six lung cancer cell lines increased proliferation in response to estradiol. We compared the effects of tamoxifen in three lung cancer cell lines. one expressing ER alpha. one expressing ER beta. and the third expressing neither of the receptors. Tamoxifen decreased proliferation and induced apoptosis which was blocked by exogenous estradiol only in the ER beta+ line. Our results suggest that proliferation of lung cancer cell lines is estrogen-independent. but that tamoxifen decreases cell growth and induces cell death by both ER-dependent and independent pathways.

Pharmacological Characterization of an Extract of Wheat Grain. E.N. Schachter. E. Zuskin. N. Rienzi. S. Goswami. V Castranova. P Siegel. M. Whitmer. G. Skloot. E. Chung. Mount Sinai School of Medicine. New York. NY.

The harvesting and processing of wheat is associated with acute and chronic respiratory disease. A water soluble extract from wheat grain (WGE) collected on a farm near Zagreb. Croatia. was prepared as a 1:10 w/v solution. The dust contained 337 g of protein/mg of dust and 1101 EU of endotoxin/mg of dust. Dose related contractions of nonsensitized. guinea pig trachea (GPT) were demonstrated using these extracts. WGE was added to the GPTs in 1/2 log dose increments. Response was measured as a percent of maximal carbachol contraction. The effects of mediator modifying drugs. as well as an angiotensin converting enzyme inhibitor (captopril). a calcium channel blocking agent (TMB8) and capsaicin were tested. Atropine inhibited WGE over the entire range of doses tested. Pyrilamine. Acivicin. NDGA. and BPB (a phospholipase A2 inhibitor) moderately reduced WGE-induced constriction. Capsaicin depleted irritant nerves of bronchoconstricting mediators. and also resulted in a modest reduction of WGE-induced constriction as did TMB8 and captopril. Indomethacin had no effect on contraction induced by WGE. We conclude that WGE exerts a non-immunologic constrictor effect on guinea pig tracheal muscle. The mechanism of this effect is complex and capable of being modulated by many mediator modifying agents. Anticholinergic agents in particular exert a profound blocking effect on this extract. GCO# 88-250ME

The Effect of Indomethacin and Pyrilamine on Airway Smooth Muscle Stretch-Induced Relaxation. K. Mrejen. G.S. Skloot. D.H. Tishler. Jourdy. I. Shpak. H. Singh. and E.N. Schachter. Mount Sinai School of Medicine. New York. NY.

Airway hyperresponsiveness in asthma may be a problem of limited smooth muscle relaxation with inspiration (Skloot et al. JCI. 1995; 96:2393). We have previously studied the response of stretch-induced relaxation (SIR) in healthy guinea pig trachea (GPT) (AJRCCM. 1998; 157:A515) in order to evaluate the role of mediators in this response. In the current study. we evaluated the role of allergic inflammation on SIR and its modulation by indomethacin (I) and pyrilamine (P).

Guinea pigs were sensitized using 3 repeated intraperitoneal injections [0.5ml of a 6mg/ml solution of ovalbumin (OA)] given over a one week period. On day 21. the guinea pigs ($n = 10$) were challenged with an aerosol of 2.5% OA. A control group of unsensitized animals ($n = 10$). followed concurrently. received a sham challenge of double distilled water. Both groups were sacrificed 24 hours after challenge. Guinea pig tracheal rings were prepared (in equal numbers) with (ep+) and without (ep-) epithelium. The rings were then suspended in physiologic buffer and maintained at a baseline tension of 2g. Individual rings were then stretched by applying a tension of 10g. After equilibration, the tissues were washed and reset to 2g tension. I (10^{-6} M), or P (10^{-5} M), or buffer was added and the response to stretch again studied. The inflammatory response in sensitized animals was confirmed histologically by the presence of extensive infiltration of eosinophils into the mucosal epithelium (not seen in controls). In **uninflamed tissue ep+**. SIR was significantly increased following the addition of P ($p<0.5$).

In **inflamed tissue ep+**. SIR was significantly decreased following the addition of P ($p<0.5$). By contrast in both inflamed and uninflamed tissue ep-. SIR remained unchanged following the addition of P. In **inflamed tissue ep+**. SIR was significantly increased following the addition of I ($p<0.5$). In contrast. in **inflamed tissue ep-**. SIR remained unchanged following the addition of I ($p<0.5$). In uninflamed tissue ep+ and ep-. SIR remained unchanged following the addition of I. These results suggest that both histamine and prostaglandins are released during SIR. by the epithelium. but they cause different responses in inflamed and uninflamed tissue.

Salmeterol Improves Static Respiratory Pressures Among Subjects with Tetraplegia. Gregory J. Schilero. MD: David R. Grimm. EdD: Ann Spungen. EdD: Erwin J. Oei. MD: Roberta Lenner. MD: William A. Bauman. MD: Marvin Lesser. MD.

Introduction: It was previously demonstrated that a beta-2 adrenergic agonist improved arm muscle strength and size among subjects with muscular atrophy secondary to spinal cord injury. It has not been determined if a beta-2 adrenergic agonist similarly improves respiratory muscle.
Design: A randomized double blind. placebo-controlled. crossover study was performed.
Methods: Salmeterol (50mcg powder: BID). a long-acting beta-2 adrenergic agonist. or placebo were administered by inhalation for 4 weeks with a 3-week washout period in-between. Maximum static inspiratory mouth pressure (PI_{max} cmH_2O). measured at residual volume. and maximum static expiratory mouth pressure (PE_{max} cmH_2O). measured at total lung capacity (TLC). were determined at baseline and during the 4th week of administration of salmeterol or placebo.
Results: Eleven healthy outpatients with tetraplegia completed the study. Mean(± SE) values for PI_{max}, PE_{max}, expiratory reserve volume (ERV). and TLC for the 11 subjects are shown in the table. Seven subjects received placebo first and 4 subjects received salmeterol first. Percent change from baseline for PI_{max} and PE_{max} for these two groups are shown in the figure.

	Baseline	Placebo	Serevent
PImax	73 ± 6	74 ± 6	81 ± 6 *
PEmax	41 ± 5	46 ± 6	51 ± 6 *
ERV (L)	0.51 ± 0.06	0.55 ± 0.05	0.60 ± 0.06 **
TLC (L)	5.20 ± 0.16	5.11 ± 0.16	5.32 ± 0.10

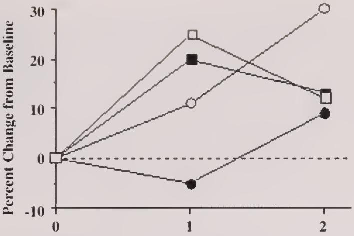
*$p<0.05$ vs. baseline and placebo
**$p<0.05$ vs. baseline

Intrepretations: Increases in PI_{max}, PE_{max}, and ERV during the salmeterol phase suggest that contractile forces generated by innervated but atrophic inspiratory and expiratory muscles improved significantly in response to the drug. Presumably, this was due to systemic absorption and the effect of the agent. Higher PE_{max} values were not due to increases in TLC, because TLC values were not significantly different during the 3 different study periods. The persistence of an elevated PI_{max} among subjects who received drug first indicates that salmeterol may have a prolonged effect on inspiratory muscle strength.
Conclusion: The generation of higher intrathoracic pressures with long-term administration of a beta-2 adrenergic agonist among subjects with tetraplegia is likely a consequence of increased respiratory muscle strength, which may improve effectiveness of airway clearance and decrease the prevalence of bronchopulmonary complications.

Rheumatology

Autoimmune Phenomena and Disease Complicating Antiviral Therapy for Hepatitis C Virus (HCV) Infection. Leslie Wilson[1], Richard Widman, Steven Dikman[2] and Peter D. Gorevic[1]. Departments of Medicine[1] and Pathology[2], Mount Sinai School of Medicine, New York, NY.

Autoimmunity is prevalent in HCV infection and may complicate combination therapy with interferon-alpha (IFNα) and ribavirin. In particular, IFNα associated autoAbs may target organ-specific antigens (eg. 21OH, GAD65, TG), although only some patients develop organ dysfunction. AutoAbs (eg. RF, ACL) may be directly linked to chronic HCV, or may be uncovered by IFNα. Occasional patients have developed systemic disease, including systemic lupus erythematosus (SLE), rheumatoid-like polyarthritis, glomerulonephritis (GN), coeliac disease, or polymyositis. We describe two cases, both men, found to have HCV Ab and RNA (0.5 – 1M copies/ml) as part of evaluations for abnormal LFTs, and liver biopsies c/w chronic HCV. Both were started on antiviral therapy, one receiving a year of IFNα before ribavirin was added because of lack of virologic response. While on combination therapy, at 16 and 24 weeks respectively, each developed severe joint pains, myalgias, fever, rash and proteinuria. Renal biopsies done to evaluate for HCV-associated renal diseases revealed instead a severe pauci-immune severe crescentic GN in one, and diffuse mesangial/focal segmental endocapillary proliferative/exudative GN (c/w lupus nephritis) in the other. Both had antineutrophil cytoplasmic antibodies, one to proteinase 3 and the other to myeloperoxidase; in addition, the second was found to have anti-Ro, RNP, dsDNA, and histone antibodies, and striking classical pathway complement activation, with depression of C2-4 and elevated levels of C3a/SC5b-9. Both had type 3 cryoglobulins (0.1 and 0.28 mg/ml respectively); however, serum and isolated cryoglobulin were consistently negative for HCV RNA by RT-PCR. Skin biopsies showed vasculitis and DE junction pathology respectively. Both patients were treated with high-dose corticosteroids, one for Wegeners granulomatosis (sinusitis, neuropathy) and the other for SLE, with gradual clinical and biochemical improvement but without recurrence of viremia, even on cytotoxic therapy. Autoimmune disease complicating therapy for HCV needs to be carefully considered in the evaluation of an expanding spectrum of extrahepatic manifestations of this infection and the use of antiviral/immunomodulatory therapy for HCV; careful virologic and serological studies, biopsy, and analysis of cryoglobulins, may elucidate the differential diagnosis in this setting, and suggest alternative treatment strategies. GCO# pending.



● = PImax (placebo 1st); ■ = PImax (Drug 1st); ○ = PEmax (placebo 1st); ■ = PEmax (drug 1st)

Spinal Cord Research

Colonic Motility during Sleep: Effect of Spinal Cord Injury. Fajardo N.R.[1], Duncan R.[2], Bauman W.A.[2], Korsten M.A.[1,3] Medicine[1] and GI[3] Programs, Bronx VAMC; Spinal Cord Damage Research Center[2], Bronx VAMC, Bronx, NY.

Background: Colonic motor activity during sleep is relatively quiescent but bursts of activity are observed during periods of arousal[1-3] However, it is not known how sleep alters the colonic motility of persons with SCI. We thus studied the effect of sleep on the colonic motility of individuals with SCI and compared it with normal subjects.
Methodology: The study was conducted on 8 subjects with SCI (mean age 59 yrs., mean duration of injury 17 years, 4 paraplegics, 4 quadriplegics), and 6 normal subjects (mean age 57 yrs.). SCI subjects all complained of difficulty with evacuation (DWE) at least once in 6 months preceding the study; all received bowel care at least three times per week. After routine bowel preparation, colonoscopy was performed (all subjects had normal examinations). After colonoscopy, the proximal end of a solid-state pressure transducer catheter (4 sensors each separated by 10 cms.) was tethered to the splenic flexure using endoclips (Olympus Corp.) as previously described by Fajardo et. al.[4]. The subjects were then allowed to carry out their usual daily activities, including sleep. Data from the catheter was recorded on a Gaeltec portable recorder. After completion of the study (which lasted for 24 hours), the data was uploaded to a computer for analysis.
Results: The motility index of subjects with SCI was significantly lower than controls during pre-sleep, sleep, and post-sleep (3.5 vs. 8.7, $p < 0.0005$; 1.4 vs. 8.8, $p < 0.005$; and 4.5 vs. 17.8, $p < 0.001$, respectively). Likewise, the motility index from pre-sleep to sleep phase was significantly decreased in the SCI group ($p < 0.008$). Both groups exhibited significant increase in motility index from sleep to post sleep ($p < 0.03$ in the control group; $p < 0.0003$ in the SCI group).
Conclusions: Colonic motility decreases during sleep both in persons with and persons without SCI. However, this decrease was found to be of greater degree in subjects with SCI. To the extent that sleep-induced depression of colonic motility slows colonic transit, our results, in part, may explain DWE seen after SCI.

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Colonic Motility in Spinal Cord Injury. Fajardo N.R.[1], Duncan R.[2], Bauman W.A.[2], Korsten M.A.[1,3]. Medicine[1] and GI[3] Programs, Bronx VAMC; Spinal Cord Damage Research Center[2], Bronx VAMC, Bronx, NY.

Background: Neurogenic bowel dysfunction is an invariable sequela of spinal cord injury (SCI)[1] and is mainly associated with difficulty with evacuation (DWE) of the bowels[2]. It has been ranked as one of the major life-limiting problems by persons with SCI[3], and its effects on quality of life after the injury is unquestionably significant. Several studies have

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shown that in SCI, large bowel transit is decreased at the level of the left colon and rectum[4], and that postprandial colonic response to food is absent[5]. Through the use of a solid state manometry catheter, colonic motility and the effect of food is compared in persons with SCI and the spinally intact (SI).

Methodology: The study was conducted on 8 subjects with SCI (mean age of 59 yrs., mean duration of injury of 17 yrs., 4 paraplegics and 4 quadriplegics), and 6 SI subjects (mean age 57 yrs.). SCI subjects all complained of DWE at least once in 6 months preceding the study; all received bowel care at least thrice/week. After routine bowel preparation, colonoscopy was performed (all subjects had normal examinations). After colonoscopy, the proximal end of a solid-state pressure transducer catheter (4 sensors each separated by 10 cms.) was tethered to the splenic flexure using endoclips (Olympus Corp.). The subjects were then allowed to carry out their usual daily activities. Data from the catheter was recorded on a Gaeltec (Medical Measurements Inc.) portable recorder.

After the completion of the study (which lasted for more than 24 hours/subject), the data was uploaded to a computer for analysis. The following 5 phases were compared: 1 hour pre-breakfast, breakfast (which lasted for 1 hour), 1 hour, 2 hours, and 3 hours post-breakfast. The significance of the differences was evaluated by Student's t-test.

Results: The results of the study showed that in all the phases included, the SCI group had significantly lower motility index, mean amplitude, and number of high amplitude waves. Likewise, during meals, the activity index, and number of waves was significantly lower in the SCI group. It was also found that in both the SI and SCI group, there is a postprandial colonic response. However, in the SCI group, the response was only seen in the descending colon and not in the rectosigmoid region.

Conclusion: Efforts to understand the effects of SCI on colonic motility are meant to address the issues that may improve DWE, thus improving the quality of life. This study is significant as it has shown that DWE is related to decreased colonic motility, and that post prandial colonic response in SCI is phasic and mainly present in the descending colon.

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Preparation for Colonoscopy in Individuals with Spinal Cord Injury.

Fajardo N.R. , Duncan R.[2], Bauman W.A.[2], Korsten M.A.[1,3] Medicine[1] and GI[3] Programs, Bronx VAMC; Spinal Cord Damage Research Center[2], Bronx VAMC, Bronx, NY.

Background: Better management of complications and improved preventive measures have prolonged the life expectancy of persons with spinal cord injury (SCI)[1-2]. It has been shown that colonoscopy improves the likelihood of early detection of colon cancer, and screening colonoscopy in individuals over the age of 50 is increasingly advocated[3]. Individuals with SCI should also benefit from this procedure but standard bowel cleansing regimen is more challenging in this group. The present study was undertaken to better define the optimal colonoscopic preparations of these individuals.

Methodology: This is a single blind prospective study on 15 patients. 3 individuals received oral sodium phosphate 45 ml. in two divided doses; 4 patients received polyethylene glycol electrolyte 4 liters solution; 8 patients were administered a combination of both. The endpoint was a satisfactory colonoscopic examination defined as visualizing the cecum without significant fecal matter. The adequacy of the colonoscopy was determined by the colonoscopist, who was unaware of the bowel preparation regimen.

Results: Patients receiving oral sodium phosphate or electrolyte lavage solution alone had poor bowel preparation which resulted in inadequate bowel visualization. Patients who received a combination of the two agents all had successful colonoscopy due to better bowel preparation.

Conclusion: In individuals with spinal cord injury, the combination of osmotic purgatives and lavage solution results in superior colonic cleansing and improved colonoscopic visualization.

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Effect of Neuromuscular Abdominal Muscle Stimulation on Defecation after Spinal Cord Injury (SCI).

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Background: Abdominal muscle contraction contributes to bowel evacuation by increasing abdominal pressure[1]. After SCI, defecatory dysfunction significantly impairs quality of life[2], in part due to impairment of abdominal muscle contraction3. Neuromuscular stimulators produce muscle contraction through the delivery of percutaneous electrical impulses. We studied the effect of the stimulation of the abdominal wall muscles on bowel evacuation of persons with SCI.

Method: This is a single blind randomized trial on 8 participants with SCI (6 quadriplegics, 2 paraplegics), all have lesions greater than T7, and all have 2 or less spontaneous bowel movements per week. The abdominal belt with implanted electrodes (Bioflex Garments, Bioflex Inc.) was fastened around the participant at the level of the umbilicus. Subjects were not informed whether or not stimulation was being applied during their bowel training, which itself was randomized. Parameters measured were time to first stool (TFS) and total bowel care time (TBC). TFS and TBC were compared in the presence and absence of neurostimulation. Statistical significance was analyzed by Student's paired t test.

Results: We found that the TFS for all subjects was significantly less with stimulation (29 mins. vs. 52 mins., $p < 0.005$). Likewise, the TBC for all subjects was significantly less with stimulation (88 mins. vs. 117 mins., $p < 0.01$).

Conclusion: The stimulation of the abdominal wall muscles significantly reduces bowel care time of individuals with SCI. If confirmed in a larger population, the use of the abdominal belt device may serve as an adjunct to the currently available methods needed for bowel care.

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Impaired Insulin-Induced Nitric Oxide Synthesis in Platelets from Spinal Cord Injury Subjects.

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Accelerated coronary artery disease (CAD) is one of the leading causes of death in individuals with spinal cord injury (SCI). Although a cluster of risk factors for atherosclerosis are known to develop in these subjects the identity of the pathologic mediators leading to the development of CAD in SCI is poorly understood. SCI individuals also demonstrate increased incidence of impaired glucose tolerance and diabetes mellitus, which suggests that insulin regulation in SCI subjects is also impaired. Recently, nitric oxide (NO) has been established to be the second messenger of insulin action (Kahn et. al., 2000).

Aims: Since insulin-induced NO production might have an important role in the prevention of CAD, through the inhibition of platelet aggregation we investigated the role of insulin-induced NO synthesis in platelets from SCI subjects.

Methods: Blood was collected in sodium citrate (0.013 M final) and washed platelets were prepared in Krebs buffer, pH 7.4, and incubated with insulin (200 µU/ml) at 23°C for 30 min. NO synthesis that was determined by the nitrate/nitrite colorimetric assay kit (Cayman Chemical).

Results: Incubation of platelets with insulin stimulated the insulin-induced NO synthesis in the control platelets (0.533 ± 0.29 vs.0.062 ± 0.02 µM over the basal level) but the SCI platelets demonstrated markedly impaired insulin-induced NO synthesis (0.044 ± 0.010 µM, $p<0.001$). As the insulin-induced NO synthesis is dependent on the binding of insulin to its receptors on the platelet surface, ^{125}I-insulin binding to control and SCI platelets was analyzed by Scatchard plot. Equilibrium binding of insulin to platelets demonstrated a curvilinear plot. Although the dissociation constants Kd_1 (1.9 nM vs. 2.3 nM) were similar, the receptor numbers (n1) were significantly reduced in SCI as compared with control (210 ± 34 vs.452 ± 56). These results suggest that platelets may be an additional site for insulin resistance. While insulin-induced NO production has been reported to be an obligatory step in the hypoglycemic effect, the impaired NO synthesis by SCI platelets may partly explain the observed disorders of the carbohydrate metabolism in SCI. In addition, impaired NO would predispose the SCI subjects to reduced vasodilation and reduced responsiveness to inhibitors of platelet aggregation. It may be postulated that the defective insulin receptors of platelets, and as a consequence, the impaired NO synthesis are probably pathophysiologically important in the pathogenesis of vascular disease in SCI.

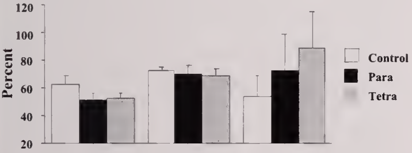
Body Composition Analysis in Persons with Chronic Spinal Cord Injury. Ann M. Spungen, EdD; Richard N. Pierson, Jr, MD; Jack Wang, MS; Joanah C. Lessey, and William A. Bauman, MD.

Background: Following the immobilization of spinal cord injury (SCI), body composition undergoes drastic remodeling. Losses in lean and gains in fat tissue mass continue during the chronic phase of SCI.
Design: A three group cross-sectional comparative design was used.
Methods: Body composition was measured by three methods: fat free mass and fat mass (FFM and FM) by dual energy x-ray absorptiometry, total body potassium (TBK) using a 4-Pi whole body counter, total body water (TBW) using tritiated water and radiolabeled sulfate (S^{35}) for segregation of extracellular water (ECW) and calculated intracellular water (ICW).

We compared a height-, weight-, age-, gender- and ethnic-matched control group (n = 19) with healthy subjects with either paraplegia (n = 32) or tetraplegia (n = 29) for differences in FFM, FM, TBK, and TBW.
Results: The group with paraplegia was older, on average, than either the tetraplegia or control groups (43 ± 13 vs. 35 ± 12 or 36 ± 10, $p<0.05$, respectively). There were no significant differences for height, weight or body mass index (BMI, kg/m²) among the three groups. The body composition results are reported in the table and figure below.

	Control (n = 19)	Para (n = 32)	Tetra (n = 29)
FFM (kg)	61.7 ± 12*	52.2 ± 10	51.8 ± 7
FM (kg)	15.9 ± 9*	24.9 ± 11	21.5 ± 11
TBK (mEq)	3826 ± 929‡	2611 ± 635	2702 ± 418
TBW (L)	44.3 ± 8*	33.8 ± 6	36.4 ± 6
ECW (L)	15.4 ± 4	13.6 ± 3†	16.4 ± 4
ICW (L)	28.7 ± 5*	20.2 ± 5	19.7 ± 5

*$p<0.005$ for Control vs. Para and Tetra, ‡$p<0.0001$ for Control vs. Para and Tetra, †$p<0.05$ for Para vs. Tetra.



FFM, TBK and TBW were lower and FM significantly higher in the two SCI groups compared with the Control group. ECW was significantly different for only the Para vs. Tetra group. The ratio of TBK/FFM was significantly greater in the Control compared to the Para or Tetra groups (62 ± 6 vs. 50 ± 5 or 52 ± 4, $p<0.0001$). No significant differences were found for TBW/FFM. The Control group had a significantly lower ECW/ICW ratio than the Para and Tetra groups (54 ± 1 vs. 73 ± 3, $p<0.01$ and 90 ± 3, $p<0.0001$, respectively). In those with SCI, duration of injury, but not age, was significantly associated with a decline in TBK/FFM ($R = -0.42$, $p<0.05$).
Conclusions: The reduced TBK per unit FFM may indicate a disproportionate loss of skeletal muscle lean tissue to visceral lean tissue. The normal TBW per unit FFM predominantly represents visceral and skeletal muscle water, which would be expected to remain unchanged. The extreme ECW/ICW fluid shift in the Tetra group is similar to that found in persons with malnutrition or low endogenous anabolic hormones.

Insulin-Induced Nitric Oxide Synthesis Is Impaired in Platelets from SCI Subjects. Nighat N. Kahn, PhD; Asru K. Sinha, PhD; and William A. Bauman, MD.

Coronary artery disease is a leading cause of death in individuals with spinal cord injury (SCI). Individuals with SCI have been reported to have a far greater prevalence of impaired glucose tolerance and diabetes mellitus. Recently, nitric oxide (NO) has been reported to be the second messenger of insulin action (Kahn, N et al., 2000). It has been recently appreciated that one of the insulin-induced platelet anti-aggregating effects is attributable to NO synthesis.
Aims: To quantitate the binding of insulin to platelets in persons with SCI. To assess whether insulin stimulated NO synthesis by platelets is reduced in persons with SCI compared to able-bodied controls.
Methods: Platelets were harvested for study from 7 subjects with SCI and 4 ambulatory controls. The determination of the specific binding of ^{125}I-insulin to platelets used the membrane filtration technique (Kahn N, et al. 1990). To stimulate production of NO, platelets were incubated with insulin at a concentration of 200 μU/ml. NO was quantitated kit assay.
Results: The specific binding of ^{125}I-insulin in platelets from subjects with SCI was significantly decreased (85%; $p<0.001$) compared with binding to normal platelets. Platelets from able-bodied controls had an insulin-induced increase of NO production (0.048 ± 0.024 to 0.525 ± 0.015 μM), whereas no effect of insulin incubation was observed in platelets from subjects with SCI (0.036 ± 0.023 to 0.047 ± 0.021).
Conclusion: These results suggest that platelets may be an additional site of insulin resistance. Absent or reduced NO production by platelets in subjects with SCI may reduce their ability to resist aggregation. In addition, diminished NO production to insulin by platelets may decrease their potential to induce a vasodilatatory response. It may be postulated that reduced platelet production of NO may be another factor in the pathogenesis of vascular disease in persons with SCI.

Soft Tissue Changes in Acute Spinal Cord Injury. Jill M. Wecht, Ed.D., Ann M. Spungen, Ed.D., Steven Kirshblum, M.D. and William A. Bauman, M.D.

Introduction: There have been few studies to date reporting soft tissue changes in individuals with acute spinal cord injury (SCI) (Wilmet, et al. 1995 & Rossier, et al. 1991). Our laboratory is currently investigating the effects of a bisphosphonate on bone mass in persons with acute SCI. There is no evidence to suggest that bisphosphonate administration will affect soft tissue.
Aim: To determine soft tissue changes in acutely injured subjects.
Methods: Seven individuals who incurred a traumatic, complete (ASIA A) transection of the spinal column at levels ranging from cervical vertebrae 4 through thoracic vertebrae 12 were studied at several time points. Data will be presented from baseline (34 ± 17; range 12–60 days post-injury) and four months (127 ± 23; range 80–147 days post-injury) after enrollment in the study protocol. The data were collected using a LUNAR DPX-IQ (LUNAR Corp. Madison, WI) and analyzed for both total body and regional soft tissue. All data are reported as mean ± SD.

		Baseline Kilogram	Percent	Month Four Kilogram	Percent
Total Body	**Weight**	68.0 ± 11.4		66.9 ± 10.7	
Total Body	**Lean**	52.5 ± 14.7	81 ± 15	47.1 ± 10.4	74 ± 13
Total Body	**Fat**	12.2 ± 10.0	19 ± 15	16.8 ± 9.2	26 ± 13
Trunk	**Lean**	24.7 ± 6.3	79 ± 14	24.1 ± 5.0	77 ± 12
Trunk	**Fat**	5.5 ± 4.6	17 ± 14	7.4 ± 4.0	23 ± 12
Leg	**Lean**	17.6 ± 7.6	78 ± 16	14.1 ± 3.7	69 ± 13
Leg	**Fat**	4.5 ± 3.4	22 ± 16	6.3 ± 2.9	31 ± 13
Arm	**Lean**	5.7 ± 1.8	77 ± 20	5.6 ± 2.0	73 ± 19
Arm	**Fat**	1.8 ± 1.8	24 ± 22	2.2 ± 2.3	17 ± 19

Summary: Mean total body lean tissue was reduced by 5.4 kilograms, a 6.7% reduction from baseline to 4 months after enrollment. This reduction in lean tissue was primarily found in the leg, which constituted a 3.4 kg loss in lean tissue (8.6%). Mean total body fat increased by 4.52 kg, (trunk = 1.94 kg and legs = 1.75 kg). Of note, percent loss in lean tissue was strongly dependent on the number of days from injury that the baseline data were obtained ($r = 0.861$, $p<0.013$), indicating a rapid loss of lean tissue within the first 4 weeks of injury with a plateau of loss thereafter.

Serum Total Testosterone Declines with Advancing Age in SCI. Run-Lin Zhang, MD; AM Spungen, EdD; RH Adkins, PhD; RL Waters, MD; and WA Bauman, MD.

In an epidemiological study, serum total testosterone (total T) declined at a rate of 0.4% per year (Gray, 1991). The effect of advancing age on levels of total T has not been reported in a large sample of individuals with SCI. We determined the total T concentrations in a large sample of men with chronic SCI (n = 172). The group was subdivided into those with paraplegia (Para; n = 93) and tetraplegia (Tetra; n = 79), complete (n = 117) and incomplete (n = 54) lesions, or by ethnicity (African-American = 22, Caucasian = 48, Latino = 98, Asian = 3). Chi square analysis was employed to assess whether a significant difference was found in the percent of younger compared with older subjects (≤40 verses >40 y) who had low total T concentrations (total T <3.0 ng/ml). This analysis also was used to determine if a difference existed in the mean age of subjects with low levels as compared with those with levels within normal limits. Linear regression analysis was used to determine the effect of age, duration of injury, level and completeness of lesion on the total T concentration. The average age of the total group was 39 ± 1 y (Par = 40 ± 1 and Tetra = 38 ± 1 y), duration of injury was 25 ± 1 y (Para = 25 ± 1 and Tetra = 25 ± 1 y), and BMI was 26 ± 1 kg/m² (Para = 26 ± 1 and Tetra = 25 ± 1 kg/m²). For the entire group, the total T concentration was 4.4 ± 0.15 ng/ml (Para = 4.7 ± 0.19 and Tetra=4.1 ± 0.24 ng/ml). Comparing the younger and older subjects, 15.2

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versus 30.1%, respectively, had low total T concentrations (p<0.02). The mean age of persons with low total T concentrations was older than it was in those with normal levels (42.6 ± 1.7 versus 37.8 ± 0.9, (p<0.02). A significant decline in total T of 0.04 ng/ml per year (0.7%/y) was found (r= –0.21; p = 0.006). There were no significant effects of ethnicity, duration of injury, level or completeness of lesion on the total T concentrations. In summary, levels of total T declined with age, in persons with SCI at a rate that appears to be increased compared with the reported decline in the general population. In this group of relatively young men with SCI, the fall in levels of total T was independent of duration of injury, ethnicity or degree of neurological impairment.

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Methotrexate-Maintained Remission in a Young Man with Polyarteritis Nodosa. M. Alam, M. Tabriz, A. Opran, and F. Rosner. Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Polyarteritis nodosa (PAN) is a rare cause of systemic vasculitis, histologically characterized by necrotizing inflammation of medium-sized or small arteries which may lead to multiple organ system disease. We describe a 22-year-old man with a large leg ulcer and flu-like symptoms who rapidly progressed to full-blown polyarteritis nodosa (PAN).
Case Report: A 22-year-old African-American man was hospitalized with a large ulcer of the right foot for debridement and possible skin grafting. The patient had root canal work and a tooth extraction four weeks earlier and was treated with ampicillin for a week. One week later he developed generalized arthralgia and myalgias without any joint swelling partially relieved with ibuprofen. He then developed a blister on his right foot, which became enlarged and ulcerated without antecedent trauma. He denied fever, chills, and cardiovascular, respiratory, gastrointestinal or genitourinary symptoms. He lost about 5 kilograms of weight.

Physical examination was remarkable for a 4 x 9 cm ulcer with clean edges, mild exudate, good granulation tissue and exposed underlying tendons and soft tissue on the dorsolateral aspect of the right foot. Another 1 x 1 cm blister was present on the dorsolateral aspect of the left foot. The remainder of the physical examination was normal.

The ulcer was debrided. The next day he developed high fever. Multiple sets of blood cultures were negative and both transthoracic and transesophageal echocardiography were normal. By the ninth hospital day the patient was still febrile. The following day multiple small palpable purpuric lesions were noted on the soles of both feet. On the 12th day the distal portion of the right first, left second and third fingers and the left second toe were found cool and cyanotic. Several 2–3 mm soft, mildly tender, subcutaneous nodules were felt on the extensor surface of the forearms. Two days later, the patient developed left-sided wrist drop and weakness of varying degrees in the radial, ulnar and peroneal nerves bilaterally, consistent with mononeuritis multiplex.

Serologic tests were negative for HTLV-1, HTLV-2, parvovirus B-19, syphilis, toxoplasma, and hepatitis A, B, C and D. There was evidence of prior exposure to cytomegalovirus. The antinuclear antibody test was positive at a titer of 1:160 with a homogenous pattern. Total CD4 lymphocyte count was 197 with a ratio of CD4:CD8 of 0.37, but both Human Immunodeficiency Virus (HIV) 1 and 2 antibodies were not detected in the patient's serum. Urinalysis was normal on several occasions. Tests for rheumatoid factor, cryptococcal antigen, cryoglobulins and lupus anticoagulant were negative. Multiple blood and urine cultures were negative. Urine and serum toxicology screens were negative. Assays for antibodies to cardiolipin, double stranded DNA, Smith, SS-A, SS-B, c-ANCA, p-ANCA, ribonucleoprotein were also negative. Complement levels (CH50, C3 and C4) were normal. Biopsy of the sural nerve was normal. Computed tomography (CT) of the abdomen and pelvis showed multiple areas of low attenuation in both kidneys, consistent with multiple microinfarcts. Selective renal angiography revealed innumerable aneurysms involving segmental, lobar and interlobar arteries of both kidneys. Diffuse irregularity with multiple stenoses and occlusions were present in the hepatic arteries, as well as in branches of the splenic artery and other arteries supplying the stomach. The diagnosis of PAN was made based on the clinical presentation of weight loss, myalgias, weakness, fever, palpable purpuric skin rash, mononeuritis multiplex, diastolic BP>100 and classic angiographic findings of multiple aneurysms and stenoses in renal, hepatic, and splenic arteries. The patient was treated with pulse methylprednisolone IV 1 gm daily for 3 days and one dose of 1gm IV cyclophosphamide (CYC) with marked clinical improvement and resolution of ischemia. After induction of remission, prednisone was slowly tapered by 5 mg every 2 weeks and daily cyclophosphamide 150 mg orally was continued. Because of concerns about the persistently low CD4 count and the known long-term side effects of CYC, the patient was switched to methotrexate 10 mg weekly, subsequently decreased to 7.5 mg per week. The patient remains asymptomatic with a low erythrocyte sedimentation rate and normal clinical and laboratory parameters. One year later, receiving only methotrexate 7.5 mg per week, the patient's repeat renal angiogram showed resolution of the aneurysms.

Conclusion: Early identification of PAN and initiation of appropriate treatment are important to avoid severe morbidity and even mortality. Low-dose methotrexate therapy may be an effective alternative treatment strategy for maintaining remission in PAN.

Choriocarcinoma in a Patient with Human Immunodeficiency Virus: Case Presentation and Review of the Literature. I. Ashley. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and the Mount Sinai School of Medicine, New York, NY.

A 26-year-old woman with choriocarcinoma and AIDS presented with hydatidiform mole and was treated with dilation and curettage. Because of persistent elevation of serum beta human chorionic gonadotropin (β-HCG), the patient was treated with combination chemotherapy for high risk gestational trophoblastic tumor. The patient did well for 14 months when her β-HCG again increased. The patient was treated with uterine curettage followed by vaginal hysterectomy. The patient was noncompliant with her chemotherapy, and later developed metastatic disease to the brain and died.

Only three other cases of human immunodeficiency virus (HIV) infection with choriocarcinoma have been reported. There is no evidence to date that gestational trophoblastic disease is more prevalent in AIDS patients. HIV infection and other immunodeficiency states, however, can lead to extensive metastatic choriocarcinoma and can influence the course of treatment in these patients. Perhaps HIV infection should be considered a poor prognostic risk factor for choriocarcinoma.

Myasthenia Gravis and Chronic Lymphocytic Leukemia. A.S. Bawa and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Myasthenia gravis is an autoimmune disease with a prevalence of 50–150 cases per million population, or approximately 25,000 persons affected in the United States. Chronic lymphocytic leukemia is the most frequent form of leukemia in adults in Western countries. The simultaneous occurrence of myasthenia gravis and chronic lymphocytic leukemia in the same person is very rare. Only ten such cases have been previously reported. We present a patient with myasthenia gravis who developed chronic lymphocytic leukemia fifteen years later.
Case Report: An 81-year-old white man with myasthenia gravis taking pyridostigmine for fifteen years presented with complaints of swellings in the neck, weight loss and malaise over the past year. No thymectomy had been done in the past. On examination, he was obese but with significant loss of subcutaneous tissue, right partial ptosis, pallor, diffuse lymphadenopathy involving cervical, axillary and inguinal regions, marked hepatomegaly, massive splenomegaly and bilateral lower limb cellulitis. His white blood cell count was 104,000 per dL with 90% lymphocytes, 6% neutrophils, 2% monocytes, 1% eosinophils, and 1% blasts. The hemoglobin was 8.8 gm per dL, hematocrit 26.3%, MCV 122 fl and platelets 154,000 per dL. Reticulocyte count was 4%, serum lactate dehydrogenase 523 U/L, and unconjugated bilirubin 1.4 mg per dL. The urine analysis was normal as were routine serum chemistry results. Chest radiography did not reveal any infiltrate, effusion, lymphadenopathy or mediastinal widening. Computed tomography of the abdomen and pelvis confirmed marked splenomegaly, moderate hepatomegaly, diffuse lymphadenopathy and cholelithiasis. Bone marrow aspiration with biopsy showed a hypercellular marrow with diffuse infiltration by small and medium sized lymphoid cells.
Discussion: Myasthenia gravis and chronic lymphocytic leukemia are diseases which involve B-lymphocytes. Both are associated with other autoimmune disorders and malignancies but they rarely occur together in the same patient. The incidence of chronic lymphocytic leukemia is higher in myasthenia gravis patients with an intact thymus compared to thymectomized patients. The same is true in rodents. The occurrence of both diseases in the same patient may represent part of the wide spectrum of B cell differentiation with both conditions having a common pathogenesis involving a defect in immune regulation or a certain genetic constitution. Alternatively, the two diseases in the same patient may be purely coincidental.

Massive Hemorrhage Following Endoscopic Resection of a Brunner's Gland Hamartoma. C. Chang and S. Chokhavatia. Department of Medicine, Mount Sinai Services at Queens Hospital Center and Mount Sinai School of Medicine, New York, NY.

Introduction: Benign tumors of the duodenum are rare (0.008%). Brunner's gland hamartomas, the benign polypoid proliferation of Brunner's glands, account for 11% of the tumors. Small lesions are asymptomatic whereas patients who present with large polyps complain of abdominal pain, dyspepsia and/or partial gastric outlet obstruction. Brunner's gland hamartomas are not premalignant lesions, and asymptomatic lesions need not be removed. Endoscopic removal is associated with post-polypectomy bleeding in 8.3% of the patients.
Case Report: A 30-year-old Chinese man was evaluated for dyspeptic symptoms. His only medication was an unknown Chinese capsule for the

treatment of hypertension. Physical examination was unremarkable. Complete blood count, routine chemistry and coagulation tests were all within normal limits. A 2 cm pedunculated, polypoid lesion was seen prolapsing from the bulb into the descending duodenum. A polypectomy snare removal was performed using a blended current. Immediate post polypectomy bleeding occurred. Hemostasis was successfully achieved with 4 cc injection of 1/10,000 units of epinephrine around the base of the stalk. The patient maintained hemodynamic stability. Twenty-four hours later, he noticed a large maroon colored stool and felt lightheaded. Emergent endoscopy showed a clear stomach and fresh blood refluxing from the pylorus. Active bleeding from the polypectomy site was seen and endoscopic hemostasis was attempted, but without success. At exploratory laparotomy, marked oozing from multiple incision sites was noted. The polypectomy site was identified via duodenotomy and was cauterized along with the other bleeding sites. Postoperatively, an extensive hematological work up, including protein C, protein S, antithrombin factor V and ANA, for a disorder of hemostasis was negative. Histologically, the polyp was described as a hyperplastic Brunner's gland. The patient's dyspeptic symptoms were controlled with a proton pump inhibitor and the hypertension was treated with a β-blocking agent.

Discussion: Asian patients frequently ingest herbal supplements. Danshen (*Salvia miltiorrhiza*), Devil's claw (*Harpagophytum procumbens*), Dong quai (*Angelica sinenesis*) and excessive garlic (*Allium sativum*) are herbs that may cause platelet dysfunction and interact with warfarin. We suspect that the diffuse oozing from multiple wound sites and the post-polypectomy bleeding in our patient was related to his ingestion of an unknown herbal medication. Physicians should inquire about herbal supplements and be cognizant of their side effects and interactions with other medications. Patients undergoing invasive interventions should discontinue herbal medications prior to their procedure.

Perioperative Dislodgement of a Dental Prosthesis. C. Chang and S. Chokhavatia. Department of Medicine, Mount Sinai Services at Queens Hospital Center and Mount Sinai School of Medicine, New York, NY.

Introduction: Foreign body ingestion may be accidental (children and elderly with impaired mental status and/or incoordination) or intentional (attention-seeking psychiatric patients). Perioperative ingestion of a dental prosthesis is rare due to strict adherence to preoperative protocols (dental history and oral examination).

Case Report: A 33-year-old multiparous Pakistani woman was hospitalized at 40 weeks and 4 days of intrauterine pregnancy for induction of labor. Three hours after admission, signs of cord prolapse were noted. The patient underwent emergent cesarian section under general anesthesia and a macrosomic baby boy was uneventfully delivered. Postoperatively, the patient could not communicate with the staff due to a language barrier. In the recovery area, she informed her husband of her missing denture, and he relayed this information to the nursing staff. The patient was still under the effect of general anesthesia but denied any respiratory distress or chest discomfort. X-rays showed the presence of a radioopaque partly metallic object overlying the gastric region. A dental consultant determined that the missing retainer bridge over tooth #6 was consistent with the x-ray findings. Informed consent was obtained from the husband and endoscopic removal of the retainer bridge from the gastric fundus was successfully accomplished utilizing a polypectomy snare. The retainer bridge consisted of a false tooth and two metallic flanges.

Conclusion: The adherence to standard preoperative protocols (dental history and oral examination) ordinarily prevents accidental dislodgment of loose teeth and dental prosthesis. This case highlights the importance of observing standard preoperative protocols even during emergencies.

Plasma Exchange in Wegener's Granulomatosis: A Case Report and Review of the Literature. H. Dhingra, A. Opran, O. Fagbami, N. Agrawal, and F. Rosner. Mount Sinai Services, Queens Hospital Center and Mount Sinai School of Medicine, Jamaica, NY.

We describe a patient with Wegener's Granulomatosis (WG) who, despite therapy with intravenous pulse methylprednisolone and cyclophosphamide, developed acute renal failure. Renal histopathologic examination demonstrated crescentic glomerulonephritis. Treatment with plasmapheresis produced dramatic clinical improvement and significant recovery of renal function.

Wegener's Granulomatosis is a systemic disease characterized by necrotizing, pauci-immune vasculitis predominantly affecting small blood vessels. WG mainly involves the upper and lower respiratory tracts and the kidneys. Before introduction of the "standard therapy" ("Fauci regimen") the prognosis of patients with WG was generally poor. The one year mortality was 80%. Renal and respiratory failure due to necrotizing glomerulonephritis and pulmonary hemorrhage were the main causes of death. However, later studies emphasize that the natural course of WG may be extremely variable, ranging from years of local disease to fulminant vasculitis with death in a matter of weeks. Thus treatment has to be adapted to the stage and activity of WG, the early aggressive therapy being mandatory when life or organ-threatening disease occurs. Our review focuses on therapeutic approaches in seriously ill patients.

Hand-Foot-Mouth Disease in an Adult. O. Fagbami, I. Tan, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and the Mount Sinai School of Medicine, New York, NY.

Background: Hand-foot-mouth disease (HFMD) is an illness commonly described in children and rare in adults. It is a febrile illness characterized by an eruptive rash involving the hands, feet and mouth. Common etiologic agents include Coxsackie viruses A16, A5, A10, B2 or B4 and Echovirus 71. A review of the literature of HFMD in adults revealed only three reported cases.

Case Report: We describe a 25-year-old woman who presented with a 4-day history of fever and maculo-papular rash involving the face, hands and feet. Her palms and soles were erythematous and very tender. Apart from a slightly increased white blood cell count, her laboratory tests were within normal limits. She received only antipyretics and gradually improved. Serology later showed increased Coxsackie A4 titers.

Conclusion: HFMD is usually associated with Coxsackie virus serotype A16 or enterovirus 71 infection. HFMD due to Coxsackie virus A4 as was proven in our patient is rare in children and even rarer in adults.

Fungal Endocarditis Presenting as a Massive Stroke. Y. Faktorova, C. Galea, A. Rozin, J. Goldstein*, and I. Sachmechi. Departments of Medicine and Radiology*, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Native valve fungal endocarditis occurs in up to 12–20% of intravenous drug abusers. More than half of patients with fungal endocarditis suffer from neurological complications secondary to cerebral emboli with typical abrupt onset of neurological deficit. We report a 40-year-old man with a history of intravenous drug abuse who presented with gradually progressing right side hemiparesis, aphasia and fluctuating changes of mental status.

Case Report: A 40-year-old man with a history of intravenous drug abuse was hospitalized with gradually progressive right sided weakness involving both upper and lower extremities, slurred speech and jerky movements of the right arm for one day. Patient had a fever of 101.4° F. He was able to follow simple verbal commands, but was drowsy with a fluctuating level of consciousness, confused and disoriented to time and place. He had Broca's aphasia, an upper motor neuron lesion of the right facial nerve, right-sided deviation of the tongue and decreased motor function of his right upper and lower extremities, which progressed to total right hemiparalysis within 24 hours. There was no pain perception on the right side of the body. The complete blood count and routine chemistry tests were within normal limits, as was his spinal fluid analysis. Head computerized tomographic (CT) scan on admission and again 36 hours later were unremarkable. Electroencephalogram revealed left hemispheric slowing consistent with left hemispheric dysfunction. Magnetic resonance imaging (MRI) of the brain showed a left-sided middle cerebral artery (MCA) infarct involving the left opercular region, left frontal and left parietal cortexes as well as lacunar infarcts in the left basal ganglia. Magnetic resonance angiography (MRA) revealed marked diminution of flow along the course of the left common carotid artery and proximal left internal carotid artery and no flow in the circle of Willis. Blood cultures grew yeast, *Candida parapsilosis*. Echocardiogram demonstrated vegetations on the aortic valve. The patient was treated with amphotericin B and had his aortic valve surgically replaced with a bioprosthetic one. Antifungal therapy with amphotericin B was continued for 5 weeks followed by fluconazole for one year. The patient remained medically stable and was transferred to an inpatient rehabilitation unit for intensive physical and speech therapy, with gradual but steady improvement.

Conclusion: The diagnosis of fungal endocarditis can be difficult and delayed because of its relative rarity and nonspecific signs and symptoms, often distant and local secondary to early embolization. Awareness of this condition, especially in high-risk groups such as intravenous drug abusers, may lead to an early diagnosis and prompt, effective management.

Intramuscular Bleeding as a Complication of Anticoagulation Treatment in a Patient with Systemic Lupus Erythematosus and Antiphospholipid Syndrome. R. Kucinsky and I. Tan. Mount Sinai Services at Queens Hospital Center and Mount Sinai School of Medicine, Jamaica, NY.

Introduction: Arterial and venous thrombotic events are responsible for significant morbidity and mortality among patients with antiphospholipid syndrome (APS). Treatment commonly consists of heparin, followed by long-term warfarin therapy (INR between 2.5 – 3.5). The advantage of anticoagulation therapy must be weighed against the risk of bleeding. We present the case of a patient with Systemic Lupus Erythematosus (SLE) and APS with intramuscular hemorrhage as a complication of anticoagulation treatment.

Case Report: A 27-year-old woman from Guyana presented with a one-day history of right calf swelling and pain that developed while she was sitting and watching TV. Pain gradually increased in severity, interfered with her ability to walk, was relieved by rest and leg elevation. There were no other associated symptoms. Patient had been diagnosed with SLE 18 months earlier when she presented with severe polyarthritis of both

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shoulders, proximal interphalangeal and wrist joints followed by discoid lesions of the face. Soon after the initial presentation the patient was hospitalized because of the sudden onset of severe headache, photophobia, lethargy, neck pain and stiffness, nausea and vomiting. She had a positive test for antinuclear antibodies (ANA 1:1280), anti DNA, anti Sm, anti histone and anticardiolipin antibodies. CT and MRI examination of the brain were consistent with central nervous system SLE vasculitis. Her medications consist of prednisone 20 mg, azathioprine 125 mg and alternating Coumadin 5 mg and 7.5 mg dose.

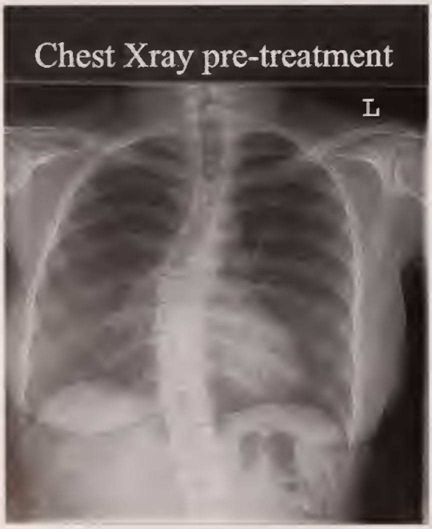
Physical examination revealed residual malar rash, right calf swelling and warmth with slight erythema and tenderness on palpation on the anterior tibial aspect and lateral part of the midcalf and a positive Homans' sign. Right calf circumference was 1.5 cm greater than the left. The stool Hemoccult test was positive. Blood biochemistry values on admission were within the normal range. Hemocoagulation tests were abnormal: aPTT >100 seconds (11.5 – 13.1), INR 7.42, PT 39.4 seconds (24.6 – 35.4). Chest X ray showed no evidence of infiltration or pleural reaction and no cardiomegaly. Doppler study of the right lower extremity was negative for deep venous thrombosis. CT and MRI of the lower extremities showed a focal collection of fluid beneath the medial head of the gastrocnemius muscle between muscle planes, a finding consistent with intramuscular hemorrhage. Coumadin was withheld for 48 hours with daily INR monitoring and again restarted on a lower maintenance dose. The patient did not require surgical intervention, blood or fresh-frozen plasma transfusion, or vitamin K supplementation. By the third hospital day the edema and pain had diminished, and the patient was discharged home. Several months later the patient was still receiving anticoagulation treatment with Coumadin. There was no further bleeding or thrombotic complications during a one-year follow-up.

Discussion: In patients with APS and SLE receiving anticoagulation therapy, the most frequent sites of severe bleeding are in the central nervous and gastrointestinal systems. Hemoperitoneum originating from ovarian bleeding is also described. It is possible that early detection of supratherapeutic INR and intervention in the anticoagulation management could decrease the short term risk and prevent bleeding complications.

Tropical Pulmonary Eosinophilia: All That Wheezes Is Not Asthma. R.A. Lopez, M. Sameen, J.K. Fleischman, and F. Rosner. Division of Pulmonary and Critical Care Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

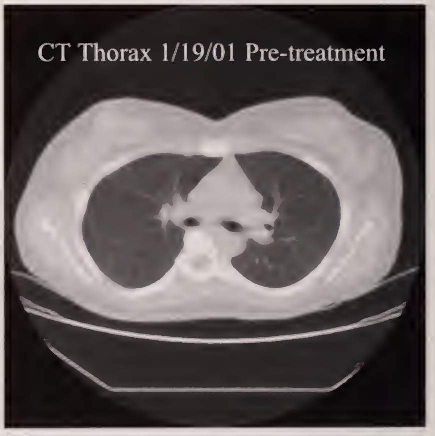
Introduction: Bronchospasm, the hallmark feature of asthma, may occur in many other conditions such as upper airway obstruction (foreign body, tumor), vocal cord dysfunction, congestive heart failure, vasculitis and eosinophilic lung disease.

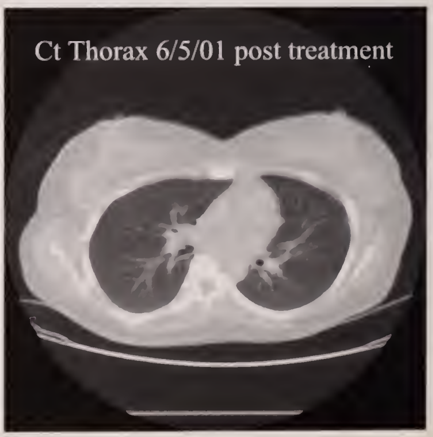
A poor response to treatment for asthma often prompts referral to a pulmonary physician. We report a case of a patient with tropical pulmonary eosinophilia (TPE) masquerading as refractory asthma for many months prior to an ultimate diagnosis after referral to our hospital.



Case Report: A 32-year-old woman was referred for evaluation of chronic cough. She had emigrated from Guyana 4 years previously and had not traveled outside the US since that time. She was otherwise healthy and took no medications. The patient's symptoms were uncontrolled for 5 months despite treatment with oral and nasal steroids and albuterol for a presumptive diagnosis of asthma. She also received multiple courses of antibiotics without improvement. Because of a poor clinical response to treatment for asthma, the patient was referred to our pulmonary medicine subspecialty clinic. Additional history of wheezing, dyspnea and a 15 lbs. weight loss over the past 6 months was obtained in the pulmonary clinic.

Physical examination revealed erythematous nasal and pharyngeal mucosa along with wheezing on forced expiration. The erythrocyte sedimentation rate was 37 mm/hr and the peripheral blood leukocyte count was 27.8 cu/mm, with eosinophils comprising 58% of the differential neutrophil count. Her pulmonary function tests revealed a mixed obstructive and restrictive ventilatory defect with reversibility after the administration of bronchodilator therapy and a decreased diffusion capacity. Although her chest x-ray was repeatedly normal (Fig. 1), computed tomography of the chest revealed a fine nodular pattern and mediastinal lymphadenopathy (Fig. 2). To further evaluate the patient's profound eosinophilia (out of proportion to the patient's asthma) anti-filarial IgG4 subclass antibody testing was performed and it was markedly positive, the normal value being <1, our patient's value >4. The patient is currently undergoing therapy with diethylcarbamazine obtained from the Centers for Disease Control and is doing well (Fig. 3).





Conclusion: Tropical pulmonary eosinophilia results from hypersensitivity to lymphatic filarial parasites found in endemic regions. Pulmonary manifestations include cough, wheezing and dyspnea and are often associated with systemic symptoms such as weight loss, fevers, and lymphadenopathy. A peripheral eosinophilia out of proportion to that which occurs in asthma is often an important laboratory clue to the diagnosis. Early diagnosis and treatment are important to prevent long-term sequelae such as pulmonary fibrosis or chronic bronchitis with chronic respiratory failure.

Retroperitoneal Leiomyosarcoma Secreting Beta-Human Chorionic Gonadotropin. I.A. Mansi, V. Glezerov, and I. Ashley. Mount Sinai Services at the Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Hormone production by non-endocrine tumors may result in a variety of paraneoplastic syndromes. Ectopic beta-human chorionic gonadrotropin hormone (β-HCG) production from leiomyosarcoma is rarely reported. We describe a patient with a β-HCG producing retroperitoneal leiomyosarcoma.
Case Report: A 57-year-old man presented with progressive abdominal pain and weight loss. A palpable, non-pulsatile, firm abdominal mass was felt below the xiphisternum down to the pelvis. Testicular examination and testicular ultrasound were normal. Computerized Tomogrophy (CT) scan of the abdomen revealed a retroperitoneal mass measuring 30 x 21 x 13 cm. The mass had areas of heterogenous attenuation, necrosis and scattered calcification. Serum beta-human chorionic gonadotropin (β-HCG) was increased (22.71 mIU/mL). On exploratory laparotomy, a large mass arising from retroperitoneal tissue was found, with a small amount of serosanguinous ascitic fluid. Histopathology confirmed the diagnosis of leiomyosarcoma. The patient was treated with doxorubicin, dacarbazine and ifosfamide. Repeat CT of the abdomen showed more cystic changes in the mass with multiple areas of low attenuation and septation. The level of serum β-HCG decreased to <0.2 mIU/mL after chemotherapy. The patient died two months later from neutropenic fever and septicemia.
Conclusion: We report a case of retroperitoneal leiomyosarcoma secreting beta-human chorionic gonadotropin. Three other cases of β-HCG secreting leiomyosarcoma (intestine, transverse colon, and spermatic cord origin) are reported in the literature. The incidence of increased serum levels of β-HCG in sarcomas is not known. The potential role of β-HCG as a tumor marker and/or in the assessment of response to therapy needs further study.

Is Laparoscopic Cholecystectomy Changing the Epidemiology of Gallbladder Disease? L. Miranda, B. Morel, and B. Pace. Department of Surgery, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Background: For more than a century, cholecystectomy had been the gold standard for the management of symptomatic gallstone disease. The first totally laparoscopic cholecystectomy (LC) was performed in 1985. Since its introduction in the US, there has been an apparent change in demographics of the patients that undergo cholecystectomy, one of the most common surgical procedures performed. Our hypothesis was that both genders are undergoing cholecystectomies at an earlier age by laparoscopy compared to laparotomy and that the learning curve influenced the patients' demographics.
Materials and Methods: This retrospective study was performed at Queens Hospital Center (QHC) in Jamaica, NY. The charts of the patients that underwent cholecystectomy between January 1992 to December 2000 were reviewed (n = 761 cases). Patients who underwent cholecystectomy during three years from the pre-laparoscopic decade, 1981, 1986 and 1991 (n = 181 cases) were randomly selected as controls. The charts of incidental cholecystectomies or those with missing codes for age and/or sex were excluded. The age and the sex of the patients were analyzed and the trend was established. The type of procedure (open, LC or conversion) was also considered for analysis.
Results: With the exception of one of the control years (1996), male patients are older than females. This tendency continues throughout the study years. The youngest patient was 12 years old (female), the oldest was 92 (female).

This chart reflects the learning curve that starts in 1992 which was the first year LC was performed at QHC. The peak of the conversions occurred in 1994 (23.7% of the cases). At the end of the study period, the percentage of conversions is 9.5 ± 1.25.
Conclusions: Despite the conventional wisdom that younger patients undergo gallbladder surgery, our study shows that the age of patients has not changed significantly in the last 20 years. The absolute number of cases has increased 130% in this population during the study period, which probably follows the national trend in the United States.

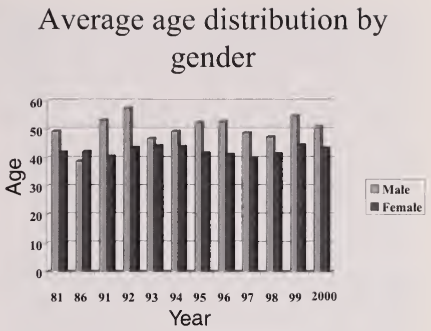
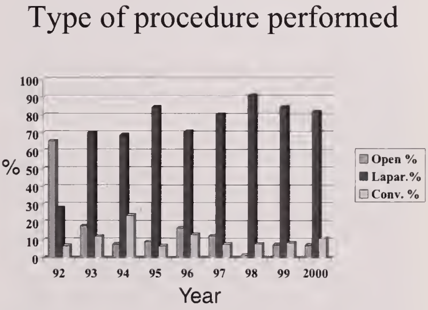


TABLE
Distribution of Average Ages from Both Genders During Control and Study Periods.

Year	Years	Total number of cases n = 942**
1981*	43.1	37
1986*	41.7	62
1991*	43.7	82
1992	45.7	75
1993	44.6	84
1994	44.9	93
1995	43.6	90
1996	44.1	85
1997	42.2	66
1998	43.3	78
1999	45.5	97
2000	44.8	93

* Control year, **Total control cases = 181



Variable AV Nodal Conduction Defect In An Adult With Systemic Lupus Erythematosus. S. Nalamasu, A. Khan, S. Liautaud, A. Onwuanyi, and I. Tan. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Introduction: Systemic lupus erythematosus (SLE) may involve the cardiovascular system in up to 50% of cases. Patients with SLE may have pericarditis, myocarditis or endocarditis and, less frequently, diverse conduction defects. Most common among the infrequently observed conduction abnormalities is first degree AV block. A few cases of high degree AV block have been reported in infants, but are extremely rare in adults with SLE. We report a case of variable AV nodal conduction defect in a patient with SLE.
Case Report: A 45-year-old Nigerian woman with SLE had AV block of variable degree quickly switching between no AV block, first-degree AV block and Wenckebach phenomenon, which spontaneously changed back to

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first degree AV block. The patient was seen in the emergency room (ER) after being called in from home for a low platelet count. The patient was asymptomatic. During a routine clinic visit one day earlier, the platelet count was 12,000/mm^3, which prompted the call in to the ER. Electrocardiogram (EKG) showed first degree AV block with a prolonged PR interval of 0.44 second. When compared to the EKG recorded the day before, the PR interval had tripled in a 24-hour period. A repeat EKG in the ER one hour later showed Mobitz type II second degree AV block with 3:1 ventricular response. Another EKG just before her admission to the CCU again showed first degree AV block with a very prolonged PR interval. She was treated with intravenous corticosteroid. The Wenckebach phenomenon did not recur. The following morning, the EKG showed first degree AV block, which resolved the following day. Thereafter, no block was observed during the follow-up visit 4 weeks later, before the patient returned to Nigeria.

Four years earlier, SLE was diagnosed in this patient because of polyarthralgia, myalgia, bruises and thrombocytopenia. The ANA test was positive (1:320 speckled pattern), as were Anti-RNP, Ro-SSA, and anti-Smith antibodies. Serum C3 and C4 levels were 61 mg/dL and 13 mg/dL respectively. At that time serial EKGs showed a pattern of normal sinus rhythm converting back and forth from first degree A-V block (with very long PR interval) to quickly resolving AV dissociation and one episode of junctional rhythm.

During the present hospitalization, the patient had no evidence of myocarditis, clinically or by laboratory values other than an increased erythrocyte sedimentation rate (with absence of fever, tachycardia, chest pain, diffuse ST-T wave abnormalities, or positive creatine kinase—MB fraction). The serum Lyme disease titer was negative. Echocardiogram did not show any organic lesion.

Discussion: The mechanism of conduction defects in patients with SLE is not understood. Some authors attribute a pathologic role to anti Ro/La antibodies, which may block the calcium channels. Other studies report conduction defects following myocarditis. More recent studies mention autonomic dysfunction in patients with SLE. There is no consensus regarding the treatment of high degree AV block. Some patients including our patient received corticosteroids and responded very well, while other patients benefited from a permanent pacemaker.

Conclusion: Conduction defects can be an isolated manifestation of cardiac involvement in SLE and may be the cause of serious morbidity. More studies are needed to determine the role of certain antibodies and to identify possible risk factors.

Interrelationship Between Thyroid Nodularity and TSH Level. S. Nalamasu[1], R. Vuppalanchi[2], and I. Sachmechi[1]. [1]Department of Medicine, Mount Sinai Services/Queens Hospital Center, Jamaica, NY, and [2]Department of Medicine, Long Island College Hospital, Brooklyn, NY.

Introduction: Several publications studying the role of Thyroid Stimulating Hormone (TSH) in goitrogenesis report conflicting results. Some studies found high TSH levels in patients with multinodular goiter, some found no difference, and yet other studies describe TSH levels to be low compared to normal controls.

Objectives: In this study, we examined the relationship between thyroid nodularity and TSH levels in patients with multinodular goiter who are clinically and biochemically euthyroid.

Methods and Materials: A survey of forty-four patients with multinodular goiter being followed in endocrine clinic was performed. Nineteen patients were chosen for the study by excluding patients with suppressed TSH (Group 1). These subjects were compared to nineteen age matched controls without any thyroid disease (Group 2). TSH levels in both the groups were obtained by review of their medical records.

Results: In group 1, TSH ranged from 0.29 – 4.65 µIU/mL with a mean of 1.45 ± 0.29. In group 2, TSH ranged from 0.38 – 1.88 µIU/mL with a mean of 1.08 ± 0.1. These values were analyzed using paired t test. The difference was not found to be statistically significant (p value of 0.22).

Conclusions: These data indicate that TSH levels in multinodular goiter are not significantly different from normal controls. More studies are needed to confirm this finding and also to investigate other possible reasons for nodularity in multinodular goiter.

Thrombotic Thrombocytopenic Purpura Associated with Clopidogrel Administration. W. Nara, I. Ashley, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Thrombotic thrombocytopenic purpura (TTP) occurs in 1 of 5,000 patients treated with ticlopidine. TTP was not observed in 20,000 patients treated with clopidogrel in clinical trials. We describe a case of TTP associated with the use of clopidogrel in a middle-aged man.

Case Presentation: A 59-year-old man complained of productive cough with white to yellow sputum for two weeks associated with pleuritic chest pain, shortness of breath and epigastric pain. His past medical history was significant for hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular accidents with complete resolution of left-sided hemiparesis and four episodes of myocardial infarctions. He had acquired immunodeficiency syndrome through sexual promiscuity with a CD_4 count of 146/µL and a viral load of 17,585 copies/µL. He did not use illicit drugs. His medications included aspirin, amlodipine, dapsone, quinapril, metformin, gemfibrozil, multivitamins, stavudine, didanosine, efavirenz, hydroxyurea, digoxin, and isosorbide mononitrate extended release.

Two weeks earlier the patient underwent percutaneous transluminal coronary angioplasty (PTCA) with stent placement for unstable angina. After intracoronary stent placement, the patient was treated with a daily oral clopidogrel (75 mg). Prior to treatment with clopidogrel, the patient's platelet count was 163,000/µL, his hemoglobin was 10.7 g/dL, and his hematocrit 31.6%.

The patient was afebrile with stable vital signs. His physical examination was remarkable for left lung basal crepitation, normal cardiovascular, abdominal and neurological examinations. His skin had no purpura or petechiae. His chest radiograph showed left basal atelectasis. Normal sinus rhythm at 84 beats/minute , left axis deviation at −51°, septal and inferolateral changes were seen on an electrocardiogram.

The white blood cell count was 4,700/µL, hemoglobin 6.7 g/dL, hematocrit of 20%, red blood cell count of 1,430,000/µL, and platelet count of 93,000/µL with a mean platelet volume of 8.1 fL. Reticulocyte count was 4.1%. Peripheral blood smear showed thrombocytopenia and fragmented, helmet shaped and schistocytic red blood cells consistent with microangiopathic hemolysis.

Coombs direct and indirect tests were negative. Serum lactate dehydrogenase (LDH) was 475 units/L, total bilirubin 1.1mg/dL and haptoglobin < 6 mg/dL. Prothrombin time (PT) was 13.1 seconds, activated partial thromboplastin (PTT) time 31.6 seconds, and the international normalization ratio was 1.13. Blood urea nitrogen was 25 mg/dL and creatinine was 1.1 mg/dL. The rest of the electrolytes were within normal limits.

The diagnosis of thrombotic thrombocytopenic purpura was made. Clopidogrel and hydroxyurea were discontinued. The patient was treated with transfusion of seventeen units of cryodepleted plasma over a period of eleven days, during which the platelet count reached a nadir of 44,000/µL. There was gradual improvement. The patient was discharged with a platelet count of 202,000/µL. Two months later the platelet count was 230,000/µL while the patient was receiving all his medications except clopidogrel.

Discussion: Clopidogrel-associated TTP has recently been described. The greatest risk occurs within two weeks of initiating therapy. The pentad of fever, renal failure, change of mental status, thrombocytopenia and microangiopathic hemolytic anemia do not all have to be present to make the diagnosis of TTP.

Other causes of TTP were less likely in this patient. The TTP resolved with discontinuation of clopidogrel. Clinicians treating patients with clopidogrel should be aware of this adverse effect.

Effect of a Troglitazone-Containing Regimen on the HbA_1C and Body Weight of Diabetic Patients. I. Sachmechi, and B. Mattam, MD. Department of Medicine, Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Objective: To retrospectively study the effects of troglitazone-containing regimens in Type 2 diabetic patients on HbA_1C and body weight.

Study Design: The medical records of 29 type 2 diabetes mellitus patients between the ages of 30 and 70 receiving troglitazone-containing treatment regimens were reviewed. Patients were assigned to 4 categories based on the treatment they were receiving. Four patients were on troglitazone only, seven were on troglitazone plus glyburide and metformin, eight on troglitazone plus insulin and ten on troglitazone plus glyburide. The HbA_1C and body weights were obtained from the charts at the start of treatment and again six months later.

Results: The mean HbA_1C and body weights at initiation of therapy and after six months of therapy and mean changes in HbA_1C and body weights in the four groups of patients are shown in the table.

Conclusions: Troglitazone-containing treatment regimens did not show a significant benefit in the reduction of HbA_1C in patients with type 2 diabetes. There was a slight weight gain (statistically not significant) in these patients after six months of follow-up.

TABLE

Groups		1 Troglitazone	2 Troglitazone Glyburide and Metformin	3 Troglitazone and Insulin	4 Troglitazone and Glyburide
HbA$_1$C	Initial	8.6 ± 0.81	8.4 ± 0.42	10.5 ± 1.04	10.98 ± 0.57
	Final	8.7 ± 1.37	8.0 ± 0.34	9.5 ± 1.01	9.8 ± 1.01
	Delta	0.10 ± 0.62	0.40 ± 0.41	0.92 ± 0.66	1.16 ± 0.71
	P Value	0.88	0.37	0.20	0.13
Body Weight	Initial	195.5 ± 24.09	204.86 ± 27.44	148.63 ± 7.25	164.90 ± 9.87
	Final	195.5 ± 26.33	214 ± 32.56	154.13 ± 9.46	169.80 ± 9.58
	Delta	0.25 ± 5.34	9.14 ± 5.25	5.50 ± 2.98	4.90 ± 2.24
	P Value	0.96	0.13	0.10	0.05

Atorvastatin Efficacy and Safety in Patients with Type II Diabetes Mellitus and Hyperlipidemia. I. Sachmechi, A. Rozin, and Y. Faktorova. Department of Medicine, Division of Endocrinology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and Mount Sinai School of Medicine, New York, NY.

Background: Atorvastatin is a synthetic HMG-CoA reductase inhibitor which decreases cholesterol synthesis.
Objective: We examined the efficacy and safety of 10 mg atorvastatin daily in reducing total cholesterol, triglyceride, and low density lipoproteins (LDL) levels and in increasing high density lipoproteins (HDL) levels in type II diabetes mellitus patients with hyperlipidemia.
Materials and Methods: Thirteen men and 9 women (age range 43 – 72 years) who were taking 10 mg of atorvastatin daily for 6 months were studied. Lipid profile, liver function tests, creatine phosphokinase (CPK) level, and hemoglobin A1c were determined before and 6 months after initiation of treatment.
Results: Of the 22 patients, 20 completed the study. Two of our patients were not compliant with the medication and are not included in the study. The baseline and post-therapy values are shown in the Table.
Conclusion: Therapy with 10 mg atorvastatin daily in patients with type II diabetes mellitus and hyperlipidemia is safe and effective in reducing total cholesterol, triglycerides and especially LDL (37.16 %) with no significant effect on the HDL level.

TABLE

	Initial	After 6 Months of Therapy	Mean Reduction	% Reduction	p* Value
Total Cholesterol (mg/dL)	205 ± 8.9	149 ± 6.3	56.50 ± 8.7	27.5%	<0.0001
Triglyceride (mg/dL)	139.3 ± 19.4	121.55 ± 17.5	17.75 ± 10.6	12.7%	0.1097
LDL (mg/dL)	133.75 ± 7.1	84.05 ± 8.2	49.7 ± 8.2	37.2%	<0.0001
HDL (mg/dL)	43.85 ± 2.5	41.45 ± 2.6	2.4 ± 1.3	5.5%	<0.0427

p* = value by paired T-test
No elevation of CPK or abnormality of liver function tests were noted.

Prostate Cancer Presenting as Paraplegia and Widespread Osteolytic Bony Metastases. S.K. Shekawat, M. Vahedi, I. Ashley, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and The Mount Sinai School of Medicine, New York, NY.

Introduction: Carcinoma of the prostate is the most common cancer in men. Metastases to the vertebrae occur in about 6.7% of patients and can severely affect their quality of life and longevity in this otherwise relatively indolent neoplasm by causing epidural spinal cord compression (ESCC). Bony metastases are mostly osteoblastic (in 97% of patients). We describe a patient with prostate cancer with multiple osteolytic metastatic lesions and complete paraplegia caused by ESCC as a presenting symptom. He also developed acute renal failure which resolved after urinary obstruction was relieved.
Case Report: A 71-year-old African-American man presented with inability to walk for two days and incontinence of urine for one day. He experienced backache and pain in his lower limbs for three months; two weeks earlier he started feeling as if walking on a sponge and, two days prior to admission, felt extreme weakness in both lower extremities and became unable to walk. In the past, the patient abused alcohol but quit following gastric ulcer bleeding twenty years earlier for which he was treated medically. His physical examination was benign except that he had an enlarged, hard but non-tender prostate gland. The stool guaiac was positive. Tendon reflexes were bilaterally absent and the patient had complete flaccid paraplegia. The examination of sensory function, mental function, speech, cerebellar function and upper limbs was normal.

Multiple x-rays of the bony skeleton showed numerous lytic lesions in the axial and proximal appendicular skeleton. Magnetic resonance imaging with T1 and T2 weighted spin echo sequences showed multiple rounded areas of abnormal signals in the vertebral bodies. A large focus of enhancement was noted within the T7 vertebral body as well as cord compression at T7 secondary to a large expansile mass. The serum prostate specific antigen (PSA) was 2615 ng/mL (normal: 0 – 4 ng/mL). The diagnostic impression was diffuse spinal metastases from prostate cancer. Widespread osteolytic lesions also suggested the possibility of multiple myeloma, which was ruled out. Serum electrophoresis was normal and Bence Jones protein testing of the urine was negative.

The patient was treated with intravenous decadron and also received 3000 cgy of telecobalt therapy covering spines T3 – T11. Blood urea nitrogen /creatinine serially increased but corrected after continuous bladder catheterization. The patient underwent prostatic biopsy of the right and left lobe which confirmed the diagnosis of prostatic adenocarcinoma-Gleason's grade 3 and 4. Several months later, some strength returned to both lower limbs. The patient has good appetite with no weight loss and is pain free. PSA three months after treatment was 0.16 ng/mL. Renal function also normalized.
Discussion: Although most prostate cancer patients have osteoblastic metastases, osteolytic lesions can occur. The onset of paraplegia usually shortens survival, but isolated case reports show prolonged survival. Recent trends in the management of patients with vertebral metastases in prostate carcinoma patients show emphasis on early detection, aggressive treatment of subclinical lesions and minimal delay in starting therapy. Moderate doses of corticosteroids are equally effective as high doses and have fewer side effects. The added modalities of radiotherapy and physiotherapy form the mainstay of management, surgery being reserved for selected cases.

Jersey City Medical Center

Radiographic Differentiation of Intraocular Glass—Evaluation of Imaging Techniques, Glass Types, Size and Effects of Intraocular Hemorrhage. J.S. Leen, R. Turbin, D. Gor, C. Kirsch, and S. Von Hagen. Jersey City Medical Center, Jersey City, NJ.

Introduction: The accurate detection of intraocular foreign bodies (IOFBs) is critically important in managing ocular trauma. The purpose of this study was to evaluate the efficacy of computed tomography (CT),

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magnetic resonance imaging (MRI), and ultrasonography (US) in detecting seven types of glass, varying in size, placed within three locations in the globe, and the effect of intraocular hemorrhage.
Methods: Glass pieces were cut in 1.5 mm, 1.0 mm and 0.5 mm and implanted on the corneal surface, anterior and posterior chambers of 42 fresh porcine eyes. Twenty-one eyes were scanned comparing axial CT, helical CT and MRI. The remaining 21 eyes were scanned by helical CT and US after implantation in a human cadaver skull before and after placement of blood in the anterior chamber (hyphema).
Results: Detection rates were 57.1% for helical CT, 41.3% for axial CT and 11.1% for T1 MRI. Results were significant with $P<0.0001$ ($n = 504$). US detected 43% of glass fragments in the posterior chamber and 24% in the anterior chamber. Detectability was greatest for green beer bottle glass (90.3%) and least for spectacle glass (43.1%, P significant at $P<0.0001$. Detection rates for six ranged from 91.7% at 1.5 mm to 48.3% at 0.5 mm, significant at $P<0.0001$. On helical CT anterior chamber glass was easiest to detect (91.7%) and corneal surface glass the most difficult (64.9%). Hyphema made no statistical difference ($P<0.0001$).
Conclusion: Helical CT was the most sensitive imaging modality for the detection of intraocular glass. The sensitivity of detection was unaffected by hyphema and determined by the glass, size and location.

The Outcome of Cardiopulmonary Resuscitation in HIV Patients in an Inner City Hospital. A. Chadha, S. Vasudevan, K. Saluja, M. Bautista, V. Thirumavalavan, and G. Cable. Jersey City Medical Center, Jersey City, NJ.

Background and Aims: The outcome of cardiopulmonary resuscitation (CPR) in HIV patients in inner city hospitals has not been well reported in literature. We aim to study the above and report our findings.
Methodology: Medical records of all patients subjected to CPR from 1996 to 1999 were studied retrospectively. The patients were divided into HIV vs. non-HIV groups. Initial success of CPR (establishment of stable rhythm with cardiac output) and final success of CPR (discharged out of hospital) were the endpoints studied. Multivariate analyses of pre-arrest and intra-arrest variables (CD4 count, duration of code, type of code, diabetes, albumin, electrolyte imbalance, functional status, sepsis and others) were done to predict final outcome and factors affecting outcome.
Results: There were total of 510 codes of which 89 were HIV infected patients. In the HIV group, 61 codes had data complete for analysis. The mean age for HIV patients were 43.3 (median 43, range 26 to 72), and in non-HIV patients was 66.9 (median 68, range 28 to 97). Mortality was 97% (65/67) in HIV patients and 94% in non-HIV patients. Nature of code was cardiac in 70% of HIV patients and 69.5% of non-HIV patients and respiratory in 10% of HIV patients vs. 5.6% in non-HIV patients. Cardiac cause of code was associated with a 78% less chance of survival as compared to respiratory cause of code in HIV patients ($0 = 0.01$). CD4 cell counts ranged from 2 to 730. For every CD4 cell count more than 10 there was a 6% greater chance of survival ($p = 0.004$). For every additional minute in duration of code there was a 6% less chance of survival. Average duration of code was 18.7 minutes in HIV patients vs. 24.2 in non-HIV patients ($p = 0.18$).
Conclusion: Contrary to published data a decade ago, we found that the CD4 count did make a difference in CPR survival. But, the overall outcome of CPR being dismal, more so for HIV patients, the increased survival associated with higher CD4 cell count, although significant in statistical terms, did not improve the overall outcome. Respiratory cause of code was more common in HIV patients and was associated with better outcome as compared to cardiac cause of code. The average HIV patient was coded 6 minutes less than his/her non-HIV counterpart, this could be a reflection of the physician's reluctance not to be persistent with resuscitation efforts in HIV patients.

Should the Pathologic Diagnosis of Chorioamnionitis Impact Maternal Care? A. Yousry, L. Applewhite, C. Strand, A. Khan, and C. Gagliardi. Jersey City Medical Center, Jersey City, NJ.

Chorioamnionitis, occurring in 1 – 5% of term and up to 25% of pre-term pregnancies, is associated with serious medical complications in both mother and newborn. Maternal complications include bacteremia (3 – 12%), wound infection (8%), and pelvic abscess (1%). Chorioamnionitis is usually diagnosed on the basis of the following clinical findings: (1) maternal fever, (2) fundal tenderness, (3) sustained fetal tachycardia > 160 bpm. The maternal significance of chorioamnionitis diagnosed solely on pathological examination of the placenta has not been fully assessed.

To determine the association between the pathological and clinical diagnosis of chorioamnionitis, the placentas of 85 consecutive patients delivered by the author were examined by the Pathology Department and the patients were assessed for clinical signs of chorioamnionitis/endometritis.

Of the 85 placentas examined, 48 (56%) were noted to have chorioamnionitis present, and 37 (44%) showed no signs of chorioamnionitis. Clinically, only 3 of 85, or 3.5% of patients exhibited signs of chorioamnionitis. The relative risk (RR) of a patient developing clinical chorioamnionitis with a positive pathology report was 1.5. The predictive value positive of pathologically diagnosed chorioamnionitis was 4%. The low predictive value positive precludes use of this as an additional modality to modify clinical practice for maternal care.

The Benefits of Imaging Studies in Alcohol Induced Acute Pancreatitis. T. Kassis, K. Ghosh, and P. Chikezi. Jersey City Medical Center, Jersey City, NJ.

Alcohol is the second most common cause of acute pancreatitis in the United States. The diagnosis usually is based on history, physical exam, serum pancreatic enzymes and imaging studies (usually abdominal ultrasound or abdominal CT scan).

It is a common practice in many hospitals to order one of these imaging studies within the first 24 hours of admission for all patients with clinically diagnosed acute pancreatitis and elevated lipase level, looking for etiology or complications, regardless of suspected etiology.

Our aim is to determine the benefit of these imaging studies during the initial 24 hours of presentation in acute pancreatitis among patients with active history of alcohol abuse. In retrospective review of the charts of emergency admission patients with acute pancreatitis, diagnoses on the basis of elevated serum amylase and lipase and clinical presentation, we identified 10 cases with an active history of alcohol abuse in which an abdominal ultrasound or CT scan (in some cases both) was done with 24 hours of admission. All patients were hemodynamically stable. None of the patients had surgical abdomen, abnormal bilirubin level or history of gallstones. The mean age of the patients (33% female and 67% male) was 42.1 years. The imaging modality was ultrasound for 79%, CT for 13% and both for 8% of the patients. Fifty-six percent of the imaging studies were reported as showing unremarkable pancreas, 41% were suggestive of pancreatitis. Three percent of the patients had gallstones with no signs of inflammation or obstruction of the pancreatic or common bile duct. None of the patients had pseudocyst or necrotizing pancreatitis. All patients were treated conservatively. No complications were reported.

In summary, our study suggested that abdominal ultrasound and CT scan are not beneficial in the initial evaluation of acute pancreatitis in hemodynamically stable active alcohol abusers.

There is a need for a prospective randomized clinical study to further evaluate these findings.

Kaposi's Sarcoma: Another Cause of Middle Lobe Syndrome. M. Bautista, D. Flores, R. Rojas, and A. Chadha. Jersey City Medical Center, Jersey City, NJ.

A 29-year-old homosexual man, a smoker, with a past medical history of HIV/AIDS, CD4 110, with disseminated Kaposi's Sarcoma (KS) was admitted for a second attempt of chemotherapy, after a frustrated first attempt with vincristine. Patient denied any recent episodes of cough, fever, dyspnea, sore throat, hemoptysis or chest pain. Physical exam was only remarkable for multiple flat and raised purple-brownish cutaneous lesions over the patient's head, trunk and extremities; and marked facial and periorbital lymphedema, with a normal lung auscultation. Chest x-ray showed prominent consolidation in the lateral segment of the right middle lobe suggestive of pneumonia, similar findings were confirmed by CT scan. Diagnostic fiberoptic bronchoscopy was performed, flat brightly red and violaceous vascular appearing lesions involving the trachea and main bronchi were observed, with increased narrowing of lateral segment of the right middle lobe bronchus. Lavage samples were obtained; no microorganism was insolated after staining and culture. Chemotherapy was started with doxurubicine and patient tolerated well. Six weeks later patient was re-evaluated, showing a significant clinical improvement of cutaneous and lymphatic lesions as well as radiographic findings, with total disappearance of previous described consolidation.
Discussion: Middle Lobe Syndrome (MLS) is an uncommon lung disorder involving the right middle lobe and/or lingula and is defined as recurrent or chronic collapse of such areas. It occurs in all age groups and is characterized by a spectrum of clinical and pathological lesions ranging from recurrent inflammatory bronchiectasis to malignant tumors. Kaposi's Sarcoma is one of the most common malignancies in the HIV/AIDS population, the lung involvement has been broadly documented by clinical and autopsy reports, but its manifestation as a solely right MLS has not been well described. KS should be considered together with lymphoma and mycobacterium infection as an etiology of MLS in the HIV population. It is also important to differentiate this entity from an active infectious process as bacterial pneumonia, since the presence of MLS secondary to neoplasmic process is likely to respond to chemotherapy and the presence of bacterial pneumonia may worsen.

Port-A-Cath Device in a Patient with HIV: A Cause of Massive Pulmonary Thromboembolism. M. Bautista, A. Rameshbabu, L. Tacsa, E. Osama, M.D., and A. Ameen. Jersey City Medical Center, Jersey City, NJ.

Indwelling central venous catheters are generally well accepted in those patients requiring frequent intravascular access to deliver parenteral medication, nutrition and for blood sampling. This popularity is due to lower cost of patient care and an acceptably low complication rate. Complications are of two types: infection and mechanical. We report a case of subtle presentation of massive pulmonary embolism (PE) mediated by a central venous catheter in a young woman with HIV.

A 27-year-old female, HIV positive with a port-a-cath placed two years previously for IV antibiotic administration, presented to the ER with sudden onset of pleuritic left side chest pain and mild shortness of breath for several hours. When initially evaluated she was asymptomatic, hemodynamically stable and the physical exam unremarkable. Chest x-ray showed normal appearance of the lungs, arterial blood gases were within normal limits, and an EKG revealed normal sinus rhythm, but rightward Axis. VQ scan showed totally absent perfusion of left lung suggestive of PE. Chest CT and echocardiogram demonstrated a 3 x 5 x 4 cm mass with soft tissue echogenicity freely mobile in the right atrium and a 2 x 3 x 4 cm similar mass occluding the left pulmonary artery. Venous Doppler ruled out deep venous thrombosis of lower limbs. IV-Heparin was started while patient remained asymptomatic and hemodynamically stable. Next day, open heart surgery was performed for the removal of the two masses, which were confirmed by pathology to be two large thrombi, and removal of the port-a-cath. Five days post-surgery the patient was able to be discharged.
Discussion: The intrusion of the catheter tip into the right atrium has been suggested as a possible mechanical complication causing intracavitary thrombogenesis, therefore increasing the risk of PE. The incidence of mural thrombi due to central venous catheter is as high as 29% in autopsy rounds, but its clinical significance as a cause of infection or embolization appear to be low. Chronic embolization with physiological adaptation is a possible phenomenon to explain the low incidence of acute fatal episodes and the subjectivity of clinical manifestation like in this case.

Malrotation and Midgut Volvulus in Childhood Period: Two Case Reports and Literature Review. P. Lianthanasarn, L. Gelvez, S. Puvabanditsin, and E. Garrow. Jersey City Medical Center, Jersey City, NJ.

The incidence of midgut malrotation is unknown. The clinical manifestations of the disease are highly variable from one patient to the other and not characteristic. Some remain symptom free throughout their whole life, some present with vomiting, some with failure to thrive and some with acute obstruction secondary to volvulus. More than 75% of children with midgut volvulus present within the first month of life or soon afterwards with vomiting, often bilious, due to intestinal obstruction. Of the remaining 25% most present with a similar clinical picture within the first two years of life and some will be erroneously diagnosed as cases of cyclical vomiting following intermittent episodes of high intestinal obstruction. These children with midgut volvulus can develop intestinal ischemia due to compression of superior mesenteric artery. This development necessitates major bowel resection and carries a poor prognosis. We present two case reports of malrotation and midgut volvulus in the early and late childhood period.

Transient Cortical Blindness Following Carotid Angiography: Evaluation by Diffusion-Weighted Magnetic Resonance Imaging. N. Khodadi, B. Maltzman, and R. Turbin. Jersey City Medical Center, Jersey City, NJ.

Introduction: Transient cortical blindness (TCB) is rare but known complication of contrast media angiography. The incidence of TCB ranges from 0.05 to 1% with highest incidence noted in cerebral angiography. Although the breakdown of blood brain barrier with direct neurotoxicity of the contrast media has been implicated, the exact mechanism remains unknown. To our knowledge, this case reports the first use of diffusion-weighted magnetic resonance imaging in evaluation of angiography contrast dye induced transient cortical blindness.
Case Report: A 63-year-old woman with high grade stenosis of left internal carotid artery underwent carotid angiography with contrast dye, Iodixanol. Immediately post angiography, the patient was found with cortical blindness. Diffusion-weighted magnetic resonance imaging obtained five hours post-angiography did not show signs of ischemia. The patient regained her baseline vision seventeen hours post-angiography.
Conclusion: By showing no evidence of acute ischemia in the occipital lobes, diffusion-weighted magnetic resonance imaging adds evidence against ischemia as a mechanism for transient cortical blindness following angiography.

Successful Treatment and Counseling of Patient with Female Genital Mutilation. A. Yousry, C. Gagliardi, and D. Campbell. Jersey City Medical Center, Jersey City, NJ.

Introduction: Female genital mutilation (FGM), a practice based on cultural and traditional patterns, has been done for the past 2,000 years. According to the World Health Organization (WHO), 80 million women have undergone this procedure. FGM is still widespread in Africa, the Middle East and Southeast Asia.
Case: A 19-year-old gravida 0 para 0 (not previously pregnant) complained of dyspareunia (since her recent marriage), dysuria and repeated urinary tract infections. She underwent FGM at the age of three. On examination, the clitoris, labia minora or the urethral orifice could not be visualized and the vaginal opening was occluded. Defibrillation was done in the OR under general anesthesia. The labia majora were surgically separated and running absorbable sutures were placed. Estrogen cream was applied for 2 weeks. Check-up revealed complete healing and, by 10 weeks, the dysmenorrhea, dyspareunia, dysuria, had resolved and her urinary stream was restored.
Discussion: FGM takes many forms including (1) removal of clitoral prepuce, (2) excision of clitoris, and (3) removal of clitoris and labia minora and occasionally much of the labia majora, suturing sides together to occlude the vagina. Complications can be both immediate (hemorrhage, shock, infection osteitis pubis) and long-term (dyspareunia, TUI, infertility, pelvic inflammatory disease [PID], psychological trauma). FGM is usually performed prior to adolescence by untrained individuals without benefit of sterile conditions or anesthesia. Patient counseling is vital to successful repair and prevention.

Hepatic Failure as the Presenting Symptom of Childhood Systemic Lupus Erythematosus: A Case Report and Review of the Literature. K. Denev and F. Pellicia. Jersey City Medical Center, Jersey City, NJ.

A 14-year-old African-American female has been transferred from regular pediatric floor to PICU because of persistent vomiting, marked drowsiness, prostration and progressive deterioration of mental status. Physical findings revealed altered mental status (stuporose), significant jaundice, asterixis, ascites and hepatomegaly in moderately obese female. The past medical history was positive for fatigue, weight loss and anorexia for the last 2 – 3 months. The teenager has also been treated for PMD for arthritis with NSAID. She denies using any other medications or illicit substances. Laboratory results demonstrated increased ammonia, transaminases and bilirubin levels, hypoalbuminemia, prolonged PT and PTT, anemia and hyponatremia with elevated protein. The patient also has positive test for ds-DNA (speckled pattern), positive AMA and ANA antibodies, antiphospholipid test. All hepatitis screening tests was well as CMV serology were negative. During the hospital stay patient sustained increase in the BUN and creatinine levels, but liver enzymes with bilirubin returned to normal. The patient was treated with lactulose, steroids (for autoimmune hepatitis), vitamin K, furosemide, multiple albumin infusions and transfusions. Several paracentesis were done suggestive of exudate and peritoneal fluid yield negative culture results. The patient underwent flexible esophagogastroduodenoscopy which revealed candidial esophagitis but no varices. The patient was transferred to St. Joseph Hospital for liver and renal biopsy. The liver biopsy demonstrated autoimmune hepatitis, renal biopsy suggestive of ATN with nephritis. 6-mercaptopurine was added to the therapy. Later on she developed seizures controlled with anticonvulsant, hypocalcaemia—symptomatically treated with Ca. Cardiac echocardiography was positive for minimal pericardiac effusion that resolved with normal LV function and normal heart anatomy. One week after discharge from St. Joseph Hospital, the patient was readmitted to Jersey City Medical Center with generalized seizures, hyperglycemia and hyperkalemia.

The final diagnosis in this case was systemic lupus erythematosus (SLE), lupus hepatitis, nephritis and cerebritis that presented initially as liver failure. This presentation of SLE is rare, unusual and particularly difficult to treat and usually has an ominous prognosis.

Transient Cortical Blindness and Retrograde Amnesia Following Cerebral Angiography: A Case Report. M. Bautista, A. Chadha, A. Mandal, T. Brannan, and S. Malik. Jersey City Medical Center, Jersey City, NJ.

Case Report: A 63-year-old Hispanic female was referred for a carotid arteriogram prior to endarterectomy due to 80-90% stenosis of the left internal carotid artery found on MRI and carotid Doppler. Past medical history was significant for hypertension, hypercholesteremia and 2 months history of amaurosis fugax. Medications included baby aspirin. Selective carotid arteriogram was done by right femoral approach and during procedure the patient had transient elevation of blood pressure (BP) to 201/101. Half an hour into the procedure patient developed sudden onset of complete loss of vision, frontal headache and confusion. After vital signs stabilization, patient was transferred to critical care unit with a BP of 160/70. Ophthalmology evaluation was unremarkable for any focal lesion and neurology exam did not show any other focal deficit. EKG revealed no new change and MRI with diffusion scan as well as CT of head were normal not showing any finding of ischemia, hemorrhage or focal accumulation of contrast media. Patient was monitored regularly and 24 hours after the event, she fully recovered vision and the headache was relieved. Amnesia was present including events up to 24 hours prior and 12 hours following the angiogram. Patient was discharged 4 days after the procedure.
Discussion: Transient cortical blindness is a rare complication after vertebral and coronary angiography. This event is usually accompanied with altered mental status, headache and/or seizures. Intravenous contrast used for the procedure has been postulated to be the causative agent. Osmotic disruption of the blood brain barrier with leakage of contrast and direct neurotoxicity is the most popular theory because of reports of accumulation of contrast in the occipital cortex. Another theory considered is vasospasm of the posterior circulation due to the neurotoxic effect of the dye. The latter seems to be the possible mechanism in our patient due to absence of abnormal findings on imaging studies, which would have supported disruption of the blood brain barrier. Spontaneous recover is usually the rule with complete resolution of symptoms unless the symptoms are due to occipital lobe embolism.

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Botryomycosis—A Bacterial Pseudomycosis. A. Chadha, S. Thamban, M. Bautista, J. Zamora, and A. Khan. Jersey City Medical Center, Jersey City, NJ.

Case Report: A 43-year-old Afro-American female presented to us with complaints of night sweats, neck mass, fever and sore throat for 3 weeks. She was diagnosed with HIV infection 5 years ago and had a CD4 count of 12 and viral load 527,000. She had opportunistic infections in past like *Pneumocystis carinii* pneumonia (PCP) and oral thrush and had been non-compliant to her anti-retroviral medications. Upon examinations, she was found to have anemia and leukopenia with significant cervical adenopathy. With a presumptive diagnosis of lymphoma she underwent lymph node biopsy. The biopsy showed abscesses with surrounding granulomatous inflammation with giant-cell reaction and clusters of bacterial organisms consistent with botryomycosis. Special stain for acid-fast bacilli (AFB) fungus and bacteria were negative. Microbiology cultures were positive for methicillin sensitive *Staphylococcus aureus*. Patient was started on anti staph treatment and on last follow-up showed improvement with resolution of symptoms and adenopathy.

Discussion: Botryomycosis has been defined as a chronic localized and progressive pseudomycosis caused by certain nonfilamentous bacteria. The bacterium most commonly isolated has been *S. aureus* although pseudomonas, *E. coli*, neisseria and other bacillus species have also been involved. In infected tissue, the bacteria characteristically form large aggregates of soft, yellow or white, spherical to lobulated grains, that are actually organized bacterial aggregates in micro colonies, which is the hallmark of botryomycosis. The integumentary form is more common, visceral rare, with isolated case reports of the nodal variety. Defective host resistance or bacteria with attenuated virulence may be key factors in persistence and aggregation of bacteria with the result the bacteria are not killed in tissue by host defenses. Commonly seen in immunocompromised patients. Histopathologic or cytologic evaluation and culture are needed to distinguish from mycetoma or actinomycosis. Usually surgery combined with prolonged IV antibiotics is needed to eradicate the infection although selected antibiotics can sometimes be used effectively.

Community-Acquired Widely Metastatic Fatal Staphylococcal Infection in Absence of Intravenous Focus: A Case Report. A. Chadha, O. El-Sayed, N. Ahmad, J. Matta, and A. Greenberg. Jersey City Medical Center, Jersey City, NJ.

Case Report: A 32-year-old African-American female was brought to the emergency department intubated due to respiratory arrest. For the last 4 months, she had been having pustules in both her axillae that came and subsided with mild temperature elevations. Three days prior to admission she developed upper respiratory symptoms with nasal stuffiness, arthralgia and myalgia that progressed and on the date of admission she became lethargic and unresponsive. In the emergency department she was in shock with fixed dilated pupils and had a burst abscess on her right chest wall. Chest x-rays showed a left middle lobe infiltrate and CT head showed a large bleed in the left parietal lobe with small bleeds in the occipital lobes with intraventricular extension. Echo showed pericardial effusion with no endocarditis. Despite pericardial window and aggressive management of shock, patient expired 18 hours after admission. The next day, two sets of blood cultures and pericardial fluid grew methicillin sensitive staph aureus, the CD4 count was 137 with HIV test negative. Autopsy showed multiple abscesses in the brain, kidneys, liver, lungs, myocardium and pericardium with no endocarditis.

Discussion: Staphylococcal septicemia with widespread metastatic seeding in the absence of endocarditis or IV focus is infrequently reported. Skin, subcutaneous tissue and surgical wound infections account for almost 50% of primary staph bacteremia that may seed peripheral organs causing secondary lesions. Gram-positive organisms can lead to a similar shock picture as in gram-negative endotoxic shock due to cell wall peptidoglycan or teichoic acid complex that triggers the release of mediators. Intra-cerebral bleed has been described as a rare complication of septicemia and is associated with adverse outcomes. It could be caused by septic arteritis or ruptured mycotic aneurysm. Direct seeding of the myocardium can lead to myocarditis with elevated cardiac enzymes mimicking myocardial infarction, as in our case, and contribute to shock. In absence of obvious focus, it can pose a diagnostic dilemma. The immune suppression observed as probably a consequence of overwhelming sepsis rather than a cause of it, although some inherent leukocyte adhesion defect or chemotactic disorder, leading to unchecked bacterial multiplication, cannot be ruled out.

Could Telangiectasias Be the Tip of the Visceral Neoplasm Iceberg? S. Prabhakar and V.S. Thirumavalavan. Jersey City Medical Center, Jersey City, NJ

Telangiectasias are permanently dilated small blood vessels with a maximum diameter of 1 mm. They have been associated with both cutaneous and systemic conditions such as pregnancy, ataxia-telangiectasia, systemic lupus erythematosus (SLE), scleroderma and cirrhosis. The following two case histories and the accompanying photographs highlight instances where the appearance of extensive dilated and tortuous intracutaneous telangiectasias preceded other symptoms suggestive of a malignancy.

A 41-year-old white male with a 15-pack year history of smoking presented with cough, hemoptysis, weight loss and shortness of breath for 2 months. Dilated blood vessels had been noticed on the anterior chest wall for more than 6 months. Physical examination revealed a superior mediastinal syndrome. Transbronchial biopsies confirmed adenocarcinoma lung of the non-small-cell type and poorly differentiated non small cell carcinoma in the supraclavicular nodes.

A 31-year-old Hispanic male with a 10-pack year history of smoking presented with right shoulder pain and anisocoria. He had noticed dilated blood vessels on the anterior chest wall for a year. CT-guided biopsy of an anterior thoracic mass confirmed non Hodgkin's lymphoma of the B cell type.

The sudden appearance of telangiectasias may thus predate other clinical symptoms of internal malignancies by several months and should prompt an active and thorough search for occult neoplasia.

Editor's Note: Pack-year = total number of years of smoking x average number of cigarettes smoked/day ÷ 20.

Association between Two Uncommon Findings in Gynecology, Endometrial Cancer and Granulosa Cell Tumor. A. Olanescu, E. Fagbongbe, G. Woroch, and J. Hutchinson. Jersey City Medical Center, Jersey City, NJ.

Introduction: Continuous unopposed estrogen (E), in either exogenous or endogenous form, is associated with an increased risk of endometrial hyperplasia and endometrial cancer (CA). Exposure to exogenous E is commonly associated with E replacement therapy without benefit of progestins. Exposure to endogenous E can be associated with either hormonal disorders or E secreting neoplasma such as Granulosa Cell Tumor (GCT).

Case: A 43-year-old G5P4 (postmenopausal for 5 years) presented with a 2-month history of vaginal bleeding. PE—normal. Ultrasound exam—endometrial thickness of 16 mm and a 3-cm simple ovarian cyst. Endometrial biopsy—complex atypical hyperplasia with foci suggestive of well differentiated adenocarcinoma. CT abdomen/ pelvis and CA-125—normal. A total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH-BSO): uterus mildly enlarged with intact serosa, right ovarian solid mass with intact capsule, multiple pelvic adhesions, no evidence of metastasis. Frozen section of ovary disclosed GCT, (6 x 5 x 4 cm), confined to capsule. Call Exner bodies and 2 – 3 mitosis/10 high-power field (HPF) were seen. Well differentiated CA of the endometrium was also present.

Discussion: Although endometrial CA occurs in less than 5% of patients with GCT, a high index of suspicion for this tumor should be present when the diagnosis of endometrial CA is made in a woman with postmenopausal bleeding and an ovarian cyst who has no other risk factors for endometrial CA. Epithelial tumor markers are not helpful, however a serum E level may help the pre-operative diagnosis of GCT.

A Live Birth with Triploidy Syndrome (69XXY). P. Lianthanasarn, R. Myers, M. Gomez, and S. Puvabanditsin. Jersey City Medical Center, Jersey City, NJ.

The Triploidy Syndrome is a well-recognized clinical entity that occurs in approximately 2% of all conceptuses. The vast majority of triploid conceptuses are aborted spontaneously before 24 weeks of gestation; thus, the syndrome is rarely seen in the neonatal period. This case report describes a live-born infant with the characteristic clinical cytogenetic findings of triploidy syndrome.

Median Cleft Face Syndrome with Lipomas of Corpus Collosum Region: A Case Report. M. Quizon, D. Akpalu, S. Puvabanditsin, and E. Garrow. Jersey City Medical Center, Jersey City, NJ.

Lipomas of the brain are rare, with 50% being situated in the corpus callosum; they are frequently associated with other developmental anomalies. Although intracranial lipomas are usually asymptomatic, they might present with epilepsy, dementia, or headache. Median cleft face syndrome is a rare form of dyshraphism that affects the midface. The syndrome has been widely referred to as frontonasal dysplasia. The types of facial clefting seen in this syndrome has been classified differently by different authors. We report a case of median cleft face syndrome that is also associated with Lipomas of the corpus callosum region. Literatures are reviewed.

Announcement of 2001 Awards

The Mount Sinai Journal of Medicine offers several prizes for manuscripts published in *The Journal* during the previous year and judged by an awards committee to be outstanding contributions to the medical literature. The committee's task certainly was formidable, but I believe that it has chosen wisely and well. The efforts of the members are much appreciated.

The Joseph Globus Award, established to honor the memory of the first and long-time editor of *The Journal*, is for the best overall paper on a clincal topic. The award goes to Douglas P. Lackey, Ph.D., for his paper "Clinical Trials in Developing Countries: A Review of the Moral Issues," volume 68 (1), pp. 4–12.

The Ralph Colp Award, in honor of the memory of a distinguished chief of surgery at The Mount Sinai Hospital, for the best paper on a surgical topic, goes to John D. Cunningham, M.D., Lester Silver, M.D., and Donald Rudikoff, M.D., for their paper "Necrotizing Fasciitis: A Plea for Early Diagnosis and Treatment," volume 68 (4 & 5), pp. 253–261.

The House Staff Award, for the best paper principally prepared and written by one or more members of the Mount Sinai House Staff, goes to Ronen Ben-Ami, M.D., Jeffrey Puglisi, M.D., Tauseef Haider, M.D., and Davendra Mehta, M.D., Ph.D., for their paper "The Mount Sinai Hospital Clinicopathological Conference: A 45-Year-Old Man with Pompe's Disease and Dilated Cardiomyopathy," volume 68 (3), pp. 205–212.

On behalf of the Editorial Staff, I am delighted to recognize the outstanding scholarship and contributions of our 2001 awardees to medicine in general, and to *The Mount Sinai Journal of Medicine* in particular.

Sherman Kupfer, M.D.
Professor of Medicine,
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Avi Fischer, Rajiv Verma, Joseph A. Gomes, and Davendra Mehta
Mount Sinai School of Medicine

Osteoporosis: Trends and Intervention
Angela M. Inzerillo and Mone Zaidi
Mount Sinai School of Medicine

Apoptosis: A Case Where Too Much or Too Little Can Lead to Autoimmunity
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Atrial Fibrillation: The Nonpharmacologic Strategy
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Veterans Affairs

In Memoriam

It is with deep regret that we announce the passing of Charles K. McSherry, a long-time member of our editorial board.

Dr. McSherry was a pioneer in the field of laparoscopic surgery for removing gallstones. A professor of surgery at the Mount Sinai School of Medicine from 1977 to 1992, he also worked and taught at New York Presbyterian Hospital and Weill Cornell Medical College. In addition, he served as director of surgery at Beth Israel Medical Center from 1976 to 1990.

Despite his busy schedule, he cheerfully agreed to join the editorial board of the ***Journal*** in 1984. At the board meetings, he would first listen carefully to the other members' opinions and then offer his own views — views that were invariably well thought out and workable.

We were honored to have Dr. McSherry as a friend and colleague, and will miss him.

Grand Rounds

Ventricular Arrhythmia:

Role of the Implantable Cardioverter Defibrillator and Radiofrequency Ablation in Addition to Drugs

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Abstract

The control of life-threatening ventricular arrhythmias in the prevention of sudden cardiac death has been a long-standing challenge to clinicians. Large-scale, randomized, controlled trials have contributed immensely to our understanding of the management of life-threatening arrhythmias. There are many causes of these arrhythmias, which occur mostly in the setting of healed myocardial infarction. Available treatments for the management of ventricular arrhythmias include antiarrhythmic drugs, implantable cardioverter defibrillators and catheter ablation. Each therapy provides unique advantages for selected patients with life-threatening arrhythmias. Because the goal of arrhythmia management is not only to provide the single best therapy but to provide the greatest assurance of symptomatic arrhythmia control, the use of combined therapy has become a standard treatment strategy for patients with sustained ventricular arrhythmias. This review will discuss the different modes of treatment available for the treatment of life-threatening ventricular arrhythmias, and their potential risks and benefits. The rationale for using hybrid or combination therapy will be presented. Finally, some of the better-known primary and secondary prevention trials for treatment of ventricular tachycardias will be reviewed.

Key Words: Sudden cardiac death, ventricular tachycardia, antiarrhythmic agents, implantable cardioverter defibrillator, radiofrequency ablation.

Introduction

Sudden cardiac death is defined as unexpected natural death, from a cardiac cause, occurring less than 1 hour after the onset of symptoms. Sudden cardiac death accounts for 300,000–400,000 deaths annually in the U.S. (1). It is the most common life-threatening manifestation of coronary artery disease and accounts for nearly 50% of the deaths attributable to cardiovascular diseases (2). The prevention of sudden cardiac death due to life-threatening arrhythmias has been a long-standing challenge to clinicians. Given the high rate of recurrence following such life-threatening manifestations, treatment is mandatory. Large-scale, randomized controlled trials have contributed immensely to our understanding of the nature and management of this condition. There are many causes of life-threatening arrhythmias, which occur in the setting of healed myocardial infarction in a region of ventricular scar (1). Other causes include arrhythmogenic right ventricular dysplasia, cardiac sarcoidosis, nonischemic cardiomyopathies, and ventricular surgery for congenital anomalies. The choice of treatment modalities for ventricular arrhythmias depends on features such as clinical presentation, left ventricular function and associated underlying etiology of the arrhythmia, and co-morbid medical conditions (Table 1).

Available treatments for the management of ventricular tachycardia (VT) include antiarrhythmic drugs, implantable cardioverter defibrillators and surgical or catheter ablation. Each therapy provides

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TABLE 1

Factors to Be Considered in Selection of Therapy for Patients with Sustained Ventricular Tachycardia

1. Type of ventricular tachycardia, documented during the arrhythmic episode
2. Symptoms during the arrhythmic episode
3. Type and severity of underlying heart disease
4. Evidence based on controlled clinical trials
5. Suitability of the patient for the theoretically optimal therapy
6. Available resources

unique advantages for selected patients with life-threatening arrhythmias. The use of antiarrhythmic agents, while noninvasive, may prevent symptomatic arrhythmia recurrences but cannot be considered curative. Implantable cardioverter defibrillators cannot prevent arrhythmia, but they are effective in reducing the risk of sudden cardiac death. The only potential cure for VT is ablative therapy. Since the goal of arrhythmia management is to provide the greatest assurance of symptomatic arrhythmia control, the use of combined therapy has become a standard treatment strategy for patients with sustained ventricular arrhythmias (3).

Antiarrhythmic Therapy

All drugs currently marketed for the treatment of arrhythmias were developed without knowledge of the specific molecular mechanisms by which their therapeutic and possible adverse effects were achieved. Understanding the chemistry of these antiarrhythmic agents and their physiological properties in animals has made it possible to develop new and more effective agents (4). Antiarrhythmic drugs have been grouped according to their common mechanism of action. This approach makes it easier for the clinician to anticipate a patient's response to a given drug. A contemporary view is that all antiarrhythmics exert their desirable effects by interacting with specific molecular targets (4). A common target is the ion channel, the pore-forming protein structure that underlies ionic currents flowing during the action potential. Drug specificity is achieved by targeting a single population of ion channels. Targeting specific cardiac ion channels, however, may result in significant proarrhythmia.

A classification system proposed by Vaughan Williams and widely used among clinical cardiologists subdivides drugs into four broad classes (5). These are: Class I – Na^+ channel blockers; Class II – β blockers; Class III – K^+ channel blockers; and Class IV – Ca^{2+} channel blockers (Table 2).

TABLE 2

Antiarrhythmic Drugs

Class	Mechanism	Drug
I	Sodium channel blocker	
A	Moderate phase-0 depression; ↓↓ retards conduction; ↓ slows repolarization	procainamide, equinidine, quinidine[1], disopyramide, moricizine
B	Less phase-0 depression; ↓ retards conduction and shortens repolarization	lidocaine, tocainide
C	Markedly depresses phase-0; ↓↓↓ retards conduction; ± effect on repolarization	encainide, flecainide, propafenone
II	β-adrenergic blocker	propanolol, others
III	Potassium channel blockers prolongs repolarization	amiodarone[2], bretylium, d-sotalol
IV	Calcium channel blocker	verapamil, diltiazem

[1] Has some Class III effects

[2] Has some effects of all classes

This classification has been criticized, because many drugs have been found to have more than one effect. For example, quinidine has both class I and III effects, while amiodarone affects all classes. In addition to these actions, these antiarrhythmic drugs may precipitate hemodynamic changes and alter neurohumoral relationships and metabolic pathways. However, a virtue of this classification system is that drugs of a common class frequently exhibit similar toxicities, most notably proarrhythmia, the cause of which may be similar for all drugs in that class (4). Studies evaluating drugs that target predominantly sodium channels (class I agents) indicate that these drugs may have unfavorable proarrhythmic effects and can lead to increased mortality (6, 7). For this reason, Class III agents, which prolong the action potential and refractoriness of cardiac tissues, have emerged as the antiarrhythmic agents of choice for managing life-threatening ventricular arrhythmias (8).

Nonetheless, the outcomes of placebo-controlled clinical trials have now unequivocally confirmed that suppression of arrhythmia, symptomatic or asymptomatic, may not necessarily decrease mortality (6, 7). Consequently, implantable cardioverter defibrillators (ICD) and radiofrequency ablation techniques have been developed to supplement the options offered by drugs alone.

Implantable Cardioverter Defibrillator (ICD) Therapy

One of the most striking therapeutic achievements has been the development of the implantable cardioverter defibrillator, which was first used successfully in 1980 (9). Implantable defibrillators are designed to deliver an electrical shock when ventricular tachyarrhythmias are detected. They can accurately and effectively terminate ventricular tachyarrhythmias in laboratory and clinical settings (9, 10). With regard to ventricular tachyarrhythmias, no other modality of treatment has had as much therapeutic impact as the ICD. Observational studies document low rates of sudden death among patients treated with implanted defibrillators, and a decreased overall mortality has been demonstrated. ICD therapy currently is clearly the most appropriate approach to mortality reduction in patients at risk for sudden death of arrhythmic origin (8).

At present, ICD therapy is the initial treatment of choice for patients resuscitated from documented ventricular fibrillation from a non-reversible cause (e.g., myocardial infarction), patients with poorly tolerated VT, and patients with impaired left ventricular function and unexplained syncope, in whom sustained ventricular arrhythmia is induced at electrophysiologic testing (1). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for ICD therapy are listed in Table 3 (11).

The use of recently improved leads enables ICD devices to act not only as cardioverter defibrillators, but as pacemakers as well, allowing backup Dual-chamber pacing, Dual-chamber sensing, Dual-chamber inhibiting (DDD) pacing on demand. This feature is useful for patients with intermittent heart block or bradyarrhythmias. Dual-chamber devices are now standard. In addition to terminating tachycardias with shocks, ICDs can terminate arrhythmias through anti-tachycardia pacing (ATP), which is painless. ICDs are multi-programmable and can be customized for each patient and each tachycardia. The ICD can be set to detect slower VTs and allow for ATP prior to the treatment of rhythm with shocks. Even the sequence of shocks can be programmed, with lower energy shocks being delivered prior to higher energy shocks.

TABLE 3
Indications for Implantable Cardioverter Defibrillator Therapy (ACC/AHA Guidelines) (11)

Class I (General agreement that treatment is beneficial, useful and effective)
Cardiac arrest due to VF or VT, not due to a transient or reversible cause
Spontaneous sustained VT
Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at EPS when drug therapy is ineffective, not tolerated or not preferred
Nonsustained VT with CAD, prior MI, LV dysfunction and inducible VF or sustained VT at EPS not suppressible by a class Ia drug

Class II (Conflicting evidence about efficacy/usefulness)
Cardiac arrest presumed to be due to ventricular fibrillation when electrophysiologic studies are precluded by other medical conditions
Severe symptoms attributable to sustained ventricular tachyarrhythmias while awaiting cardiac transplantation
Familial or inherited condition with a high risk for life-threatening ventricular tachyarrhythmias such as long QT syndrome
Nonsustained VT with CAD, prior MI, LV dysfunction and inducible sustained VT or VF at EPS
Recurrent syncope of undetermined etiology in the presence of ventricular dysfunction and inducible arrhythmias at EPS when other causes of syncope have been excluded

Class III (Evidence that treatment is ineffective and in some cases may be harmful)
Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmia
Incessant VT or VF
VF or VT resulting from arrhythmias amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with Wolff-Parkinson-White syndrome, RVOT VT, idiopathic LV VT, or fascicular VT)
VT due to a transient reversible disorder (e.g., MI, drugs, trauma, electrolyte disturbance)
Significant psychiatric illness that may be aggravated by ICD implantation or may preclude systemic follow-up
Terminal illness with life expectancy ≤ 6 months
Patients with CAD and LV dysfunction with prolonged QRS duration in the absence of spontaneous or inducible sustained or nonsustained VT who are undergoing coronary bypass surgery
NYHA class IV drug-refractory CHF in patients who are not candidates for cardiac transplantation

CHF = congestive heart failure
VF = ventricular fibrillation
VT = ventricular tachycardia
EPS = electrophysiological study
CAD = coronary artery disease
MI = myocardial infarction
RVOT = right ventricular outflow tract

Although implantable cardioverter defibrillators are effective in terminating ventricular tachyarrhythmias and preventing sudden cardiac death, patients with defibrillators often receive appropriate shocks triggered by ventricular tachyarrhythmias as well as inappropriate shocks triggered by supraventricular tachyarrhythmias. Moreover, ICDs do not provide absolute protection against death from arrhythmia, since about 2% of episodes of ventricular tachyarrhythmias are refractory to appropriate defibrillator therapy (12). Administration of antiarrhythmic therapy as an adjunct to ICD may reduce the number of recurrent episodes and the defibrillation threshold, and improve responsiveness to shocks (13).

Recent studies suggest that episodes of ventricular fibrillation, even ones that are successfully terminated by implantable cardioverter defibrillators, may increase the risk of myocardial (14, 15) and cerebral ischemic (16, 17) injury. The avoidance of frequent shocks is crucial for the safety and quality of life of patients with ICDs. An important complication of shocks delivered by implantable defibrillators is that they may evoke serious psychological reactions in as many as one third of these patients (18, 19).

VT Mapping and Ablative Therapy

Studies suggest that ventricular tachyarrhythmias occurring in the setting of structural heart disease are due to a reentrant mechanism (20). The ability to reproducibly initiate and terminate VT with programmed ventricular extrastimuli is considered the *sine qua non* of reentry (21). Sustained monomorphic VTs can be due to reentry involving an area of scar, macro-reentry through the bundle branches, and focal automaticity. Scar-related reentry is the most common cause of VT in patients with heart disease. Reentrant VT typically exists as a "figure eight" with clockwise and counterclockwise rotation of wavefronts that share a central isthmus or diastolic pathway. During tachycardia these pathways are protected by lines of block, the integrity of which is crucial for sustaining the VT. There is evidence that even small changes in the conduction characteristics of these pathways or their morphology can terminate the VT (22). Most VT circuits have a subendocardial location, so that a percutaneous approach can be performed without general anesthesia. However, catheter mapping and ablation of VT remain relatively high-risk procedures, with a 10% overall complication rate (23, 24), including a 1–2% rate of procedural mortality (25). An overall approach to VT ablation is illustrated in Fig. 1. Indications for catheter ablation of ventricular tachyarrhythmias can be seen in Table 4. Mapping can be performed during VT and during sinus rhythm, with identification of regions of scar based on mid-diastolic, low-amplitude and low-voltage electrograms (Fig. 2). Conventional mapping techniques involve pacemapping during sinus rhythm to reproduce an electrogram identical to that of the VT (26) (Fig. 3) and entrainment[1] techniques during VT to confirm the presence of a site located within the diastolic pathway (22). However, segments that do not participate in the reentrant circuit often may exhibit diastolic activity, leading to low sensitivity and specificity of pacemapping in the presence of infarct scar (26, 27). Concealed entrainment[2] is demonstrated in only 54–60% of VTs (27, 28)

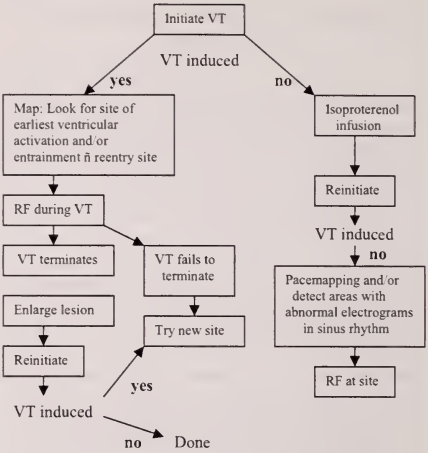

Fig. 1. An algorithm showing how to approach considering VT ablation.

TABLE 4

Indications for Radiofrequency Catheter Ablation in Patients with Ventricular Tachycardia

Catheter Ablation Is the Suggested First-Line Therapy:
- Idiopathic VT: right ventricular outflow tract tachycardia, fascicular tachycardias
- Bundle branch reentry in patients with cardiomyopathy (VT has LBBB-like morphology)

Catheter Ablation Should Be Considered:
- VT in the setting of CAD with multiple ICD shocks
- Slow, incessant VT resistant to multiple medications

No Consistent Data to Suggest Its Efficacy: Ablation Should Not Be Performed
- Arrhythmogenic RV dysplasia
- Dilated Nonischemic Cardiomyopathy

LBBB = left bundle branch block
RV = right ventricle

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[1] **Entrainment** is the capture of a reentrant circuit through pacing. The response rate of the circuit, when entrained, is equal to the rate of pacing when pacing at a rate faster than that of the intrinsic tachycardia. The arrhythmia terminates with abrupt cessation of pacing or with pacing at a rate slower than that of the intrinsic tachycardia.

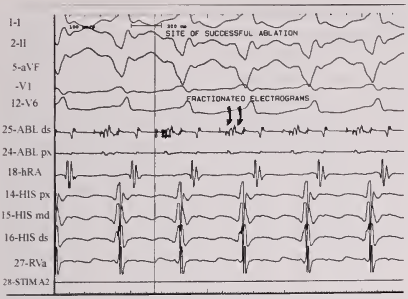

Fig. 2. From top to bottom: limb leads I, II, aVF; precordial leads V1,V6; intracardiac electrograms from distal (ABL ds) and proximal (ABL px) ablation catheter, high Right Atrium (hRA), HIS proximal (HIS px), mid (HIS mid) and distal (HIS ds) and Right Ventricle (RVa). Bold arrows show fractionated electrograms in mid-diastole (endocardial recording) at the site of slow conduction. The horizontal bar shown in Lead I represents an interval of 200 milliseconds.

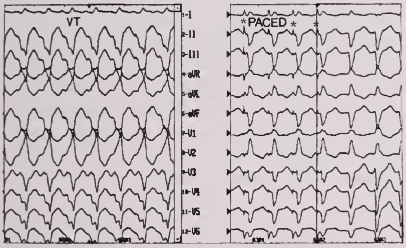

Fig. 3. 12-lead ECG of clinical VT can be seen in the left panel. In the right panel, the first 4 beats are paced (note pacing artifact *), with a QRS morphology identical to the clinical VT (last 3 beats) (no pacing artifact present).

even with the most successful mapping technique for identifying critical regions for ablation. Moreover, when acute ablation is successful, long-term recurrence rates range from 15–50% (23, 24, 29).

The morbidity and mortality of cardiac disease are due, in large measure, to its underlying severity. Patients with scar-related VTs have an average of three different morphologies of inducible VT at electrophysiologic testing (23, 29). Multiple VT morphologies can be due to multiple reentry circuits that originate from a single region such that ablation of one area may abolish more than one VT. Difficulty in mapping the complex morphology and location of the diastolic pathway is reflected by the frequent failure to eradicate VT in patients with multiple morphologies and the high rates of recurrence of acutely ablated VT. Conventional mapping techniques lack spatial resolution due to the limited number of contact electrodes available, and considerable time is required for mapping at sequential endocardial points.

To overcome these limitations, rapid, high-resolution systems have been developed which map an entire cardiac chamber to identify spatial and temporal relationships critical for maintaining VT (22). Complex ventricular arrhythmias can now be treated even if multiple VT morphologies are present, with high success rates and some of the lowest recurrence rates of targeted VT to date (22, 25). Continued improvements in the computational process of electrogram reconstruction, accuracy of geometry formation, 3-D modeling, and navigation may further improve the results of VT ablation and make the technique more generally available.

Hybrid Therapy

Optimum arrhythmia management has evolved so that the best available management strategies can be combined to reduce or eliminate the risks associated with arrhythmia. Using the combination of catheter ablation and ICDs, or antiarrhythmics and ICDs, may result in greater reduction in the recurrence rate of significant ventricular tachyarrhythmias. This approach has now been accepted as the standard of care (3).

Ablation and ICD

The rationale for combining these modalities stems from several important considerations. Following ablation, the response to programmed stimulation is used to judge its efficacy. However, studies that have assessed the reproducibility of the response to programmed stimulation, or its value in predicting arrhythmia-free survival in patients treated with antiarrhythmic agents, raise considerable doubt about the predictability of the clinical outcome after catheter ablation (30–32). Additionally, the endpoints defining success of catheter ablation for VT in the setting of structural heart disease vary, and the long-term outcomes related to these endpoints have not been determined. The

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[2] **Concealed entrainment** is confirmed by pacing at a rate faster than the intrinsic tachycardia, resulting in an ECG and intracardiac activation identical to the intrinsic tachycardia (see Fig. 3). It occurs as a result of pacing from a site that is orthodromically distal to the area of slow conduction in a reentry circuit, from a site that is distant from the reentry circuit, or from an area of slow conduction in the reentrant circuit.

evolution of ICD and lead technology has resulted in a dramatic reduction in the risk related to implantation of these devices (3). Moreover, studying the efficacy of ablative therapy for VT through the stored diagnostic information in the ICD has great potential for providing important diagnostic information. Indeed, the efficacy of any new antiarrhythmic therapy used for the treatment of ventricular arrhythmias can only be determined in patients with an ICD. Finally, for those patients in whom frequently recurrent VT is not suppressed by antiarrhythmic agents, ablation may serve as an adjuvant therapy to the ICD (3) (Fig. 4).

The disadvantages of combining these modalities include altered pacing thresholds in areas adjacent to endocardial leads and the potential need for additional ICD testing and resetting of antitachycardia pacing features due to changes in VT characteristics as a result of ablative therapy (3).

ICD and Antiarrhythmics

Antiarrhythmic agents remain an important adjuvant to ICD therapy, despite a trend toward less use in patients with ICDs, particularly in those patients presenting with cardiac arrest (33). Antiarrhythmic agents are used to prevent recurrences of arrhythmia and potentially reduce other supraventricular tachycardias that may induce inappropriate shocks from the ICD. Additionally, the use of antiarrhythmics may make the tachycardia amenable to ablative therapy and may reduce the defibrillation threshold. Over the last several years the use of amiodarone and sotalol has increased, while the use of class I agents has decreased. Class III agents, with the exception of amiodarone, have been shown to decrease the defibrillation threshold (34, 35).

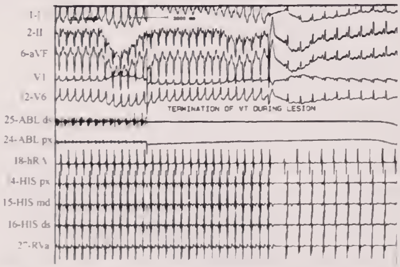

Fig. 4. From top to bottom: limb leads I, II, aVF; precordial leads V1,V6; intracardiac electrograms from distal (ABL ds) and proximal (ABL px) ablation catheter, high Right Atrium (hRA), HIS proximal (HIS px), mid (HIS mid) and distal (HIS ds) and Right Ventricle (RVa). Radiofrequency lesions led to termination of VT after the onset of radiofrequency ablation. The horizontal bar shown in Lead I represents an interval of 2000 milliseconds.

One should be aware of potential adverse reactions when using antiarrhythmics. Class I agents and amiodarone have been associated with an increase in the defibrillation threshold (36). Class I agents also may produce a cycle-length-dependent increase in pacing threshold (37). Slowing the rate of the VT, as occurs with many antiarrhythmic agents, may result in a tachycardia below the rate cut-off for the device. Slowing the sinus rate may result in increased device use via bradycardia pacing.

The well-known proarrhythmic effects of antiarrhythmic drugs may be important. Occasionally, a predictable QT prolongation is noted. However, potentiation of spontaneous arrhythmias, in the absence of surface ECG characteristics such as QT prolongation, may result from alterations in refractoriness due to antiarrhythmic drugs.

Trials

The role of antiarrhythmics and implantable defibrillators for the treatment of ventricular tachyarrhythmias has been studied extensively over the past decade. Some of these trials have had a major impact on the way VT is currently treated. The following is a brief review of some of the primary and secondary prevention trials.

Primary Prevention Trials

CAST: The Cardiac Arrhythmia Suppression Trial (6)

The rationale for CAST was based on the assumption that suppression of asymptomatic ventricular premature depolarizations, a risk factor for sudden death after MI, by chronic antiarrhythmic therapy, would reduce arrhythmic death. Eligible patients had reduced ejection fractions and more than 6 ventricular premature depolarizations/hour. The drugs tested were encainide, flecainide and moricizine. Patients were given "the best drug" based on suppression of ventricular ectopy in an open-label phase. The CAST Data and Safety Monitoring Board recommended that encainide and flecainide be discontinued because of increased mortality from arrhythmia. The study continued with moricizine (CAST II). CAST II was also stopped prematurely due to increased arrhythmic death in the drug treatment population (38).

GESICA: Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (39)

This study looked at the use of low-dose amiodarone as primary prevention against sudden death in patients with severe congestive heart failure

(CHF — ejection fraction less than 35%, NYHA classes II, III, and IV). In this population of patients, sudden cardiac death accounts for more than 40% of all deaths. Patients were not being treated with β-blockers and were randomized to receive amiodarone or no therapy. The primary endpoint was total mortality rate, with secondary endpoints of sudden death, progressive heart failure and hospitalization for heart failure. There was a relative-risk reduction in total mortality of 28% in the amiodarone- treated group, which appeared to stem from an early (30-day) reduction in sudden death followed by a later decrease in deaths from progressive heart failure. Interestingly, in this study, amiodarone reduced the total mortality rate without significantly reducing deaths from arrhythmias.

STAT-CHF: Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (40)

Like GESICA, this study examined the effects of amiodarone in patients with CHF (ejection fraction less than 40%). Unlike GESICA, in which only 39% of the patients had coronary artery disease with a prior myocardial infarction, this study enrolled a greater number of patients with ischemic heart disease (72%). The primary endpoint was total mortality rate. The rate of sudden death was not decreased by amiodarone in this study, and there was no significant survival benefit for patients in receiving amiodarone versus placebo. However, in nonischemic heart disease patients (like those in GESICA), a trend favoring amiodarone was noted.

SWORD: Survival with Oral D-Sotalol Study (41)

SWORD attempted to prevent death by using an antiarrhythmic agent in patients at high risk for sudden cardiac death. At the time of this study, the detrimental effects of class I agents in these patients were well known from the CAST trial. Amiodarone, a class III agent, was thought to have a neutral or positive effect in preventing sudden cardiac death. It was hoped that other class III drugs, without the potentially serious adverse effects of amiodarone, would be effective in preventing sudden death. d-sotalol is a pure class III antiarrhythmic agent and lacks the β-blocking effects of d, l-sotalol. This property of d-sotalol may increase its tolerability in patients with left-ventricular dysfunction.

SWORD was a placebo-controlled, randomized study assessing the effects of d-sotalol on the total mortality of patients with a previous myocardial infarction (MI) and reduced left ventricular function. Patients were eligible if they had a previous MI and an ejection fraction less than 40%. QT interval was monitored closely and the study drug was discontinued if the QT interval exceeded prespecified limits. The primary endpoint was all-cause mortality; the secondary endpoint was cardiac mortality.

The trial was stopped prematurely when it became evident that there were excess deaths in the d-sotalol group. However, there was no excess in serious arrhythmic events or torsades de pointes in the d-sotalol group and few objective data to implicate torsades de pointes or proarrhythmic effects as causes of the increased mortality (42). Interestingly, the adverse effects of the drug were more pronounced in female patients and in patients with an ejection fraction of 30% or greater.

MADIT: Multicenter Automatic Defibrillator Implantation Trial (43)

This was the first trial to study the prophylactic use of implantable cardioverter defibrillators to prevent sudden death from ventricular tachyarrhythmias. The patients were a high-risk group with prior MI, low left ventricular ejection fraction (LVEF) and inducible ventricular arrhythmias. Eligibility criteria included having a myocardial infarction more than 3 weeks prior to enrollment, asymptomatic nonsustained VT and an LVEF less than 35%. There was no placebo arm, but a "conventional therapy" arm was used. The primary endpoint was death from any cause.

After more than 5 years of enrollment, the study was stopped prematurely because superiority of the ICD had been demonstrated. There was no evidence that the use of antiarrhythmic medications or any of the baseline variables of the patients had any influence on the risk of death. In addition, shock discharge occurred in 60% of defibrillator patients within 2 years after implantation.

This study has been criticized for several reasons. After 63 months of enrollment at 32 centers, only 196 patients were enrolled. Additionally, the "conventional therapy" was actually unconventional, with barely half of the patients receiving an angiotensin-converting enzyme (ACE) inhibitor, a β-blocker, or amiodarone.

EMIAT: European Myocardial Infarct Amiodarone Trial (44)

This study examined the use of amiodarone as primary prophylaxis in patients at high risk for death after an acute myocardial infarction. Patients with a documented MI and an ejection fraction less than 40% were randomly assigned to placebo or amiodarone. The primary endpoint was death from any cause, with secondary endpoints of cardiac death, arrhythmic death and arrhythmic death plus resuscitated cardiac arrest. Once again, amiodarone failed to improve survival of patients at high risk of sudden cardiac death.

There was no difference in the all-cause mortality between the treatment groups. However, there was a trend toward reduction in arrhythmic death in the amiodarone group and a significant reduction in the combined endpoint of arrhythmic death and resuscitated cardiac death in the amiodarone group. The reduction in arrhythmic death in the amiodarone group was offset by increases in nonarrhythmic and noncardiac mortality rates. This emphasizes the importance of total mortality rate as an outcome measure in cardiac arrhythmia trials.

CAMIAT: Canadian Myocardial Infarct Amiodarone Trial (45)

The inclusion criteria for this trial were more restrictive than those of EMIAT because of the requirement for spontaneous ventricular ectopy. Patients in this study needed to have at least 10 premature ventricular contractions (PVCs) or at least one run of VT. Unlike EMIAT, the primary endpoint was the composite of resuscitated ventricular fibrillation (VF) or arrhythmic death. Secondary outcomes included arrhythmic death, cardiac death and death from any cause. A high proportion of patients (60%) were taking β-blockers at enrollment, with an even higher proportion at later phases of the trial. By an intention-to-treat analysis, the primary endpoint of resuscitated VF or arrhythmic death was reduced by amiodarone, but the event rate in both groups was low. This study, however, did not use total mortality rate as an endpoint, and the study used a one-sided test of significance which assumes that the use of amiodarone can only be beneficial or neutral if used in this group of patients.

CABG Patch: The Coronary Artery Bypass Graft Patch Trial (46)

This trial tested the hypothesis that prophylactic implantation of a defibrillator at the time of bypass surgery would improve long-term survival of patients at high risk for sudden death. This study included patients with a reduced left-ventricular ejection fraction and an abnormal signal-average-ECG (SAECG), a predictor of increased mortality. Of the patients enrolled, 55% had three-vessel coronary artery disease, 83% had a prior MI, 60% were taking an ACE inhibitor and almost 20% were taking a β-blocker.

Prophylactic implantation of an ICD did not improve survival in this study. An explanation for this may be the potential reduction in ischemia and therefore sudden death, as well as the improvement in LV function in these patients, as a result of revascularization.

MUSTT: Multicenter Unsustained Tachycardia Trial (47)

The ability to guide antiarrhythmic therapy as the result of electrophysiologic (EP) testing in patients at high risk for sudden death was evaluated in this study. Patients included in the study were similar to those in MADIT in that they had coronary artery disease, left-ventricular dysfunction and nonsustained VT. However, more data regarding the inducibility at electrophysiologic testing and responsiveness to antiarrhythmics were obtained in patients enrolled in this study. Patients enrolled had coronary artery disease, and LVEF less than 40%. They underwent electrophysiologic testing with the following endpoints: reproducible induction of sustained VT, reproducible induction of more than 15 complexes of polymorphic VT or ventricular flutter, or noninducibility. Patients who were inducible then were randomized to antiarrhythmic therapy guided by EP testing or no antiarrhythmic therapy. Drugs were assigned randomly, except that amiodarone could only be considered after two failed drug trials. If no drug could be found to prevent inducibility, then a drug that resulted in hemodynamic stability during VT induction could be utilized. ICD therapy could be used after one failed drug trial. The primary endpoint was arrhythmic death or resuscitated cardiac arrest. Secondary endpoints included death from all causes, cardiac death and spontaneous, sustained VT.

In this study, the total mortality in the EP-guided arm was 24% in the ICD-treated patients versus 55% for drug-treated patients and 48% for patients receiving no therapy. The investigators determined that the reduction in total mortality was attributable almost entirely to the use of an ICD in the EP-guided arm. An important lesson from this study is that patients with coronary artery disease, decreased LV function and inducible sustained VT at EP testing, comprise a group of patients at high risk for sudden death and that this risk is reduced substantially by ICD implantation.

Several Trials that Are Still Ongoing

SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial

This trial is enrolling patients with LVEF less than 35%, class II, III, IV, and congestive heart failure for more than 3 months from either ischemic or nonischemic causes. There are no arrhythmia markers included in the eligibility criteria. All patients will be treated with optimized heart failure regimens including afterload reduction, β-blockers and diuretics. Patients will be randomized for adjunctive therapy with placebo, amiodarone or an ICD. The primary endpoint is death from any cause.

DEFINITE: Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation Trial

This study focuses on patients with a dilated cardiomyopathy of nonischemic causes. Eligibility criteria include a nonischemic cardiomyopathy with a left ventricular ejection fraction of less than 35%, and either nonsustained VT on Holter monitoring or telemetry monitoring or more than 10 PVCs/hour on Holter monitoring. Patients will be assigned to conventional heart-failure treatment with or without an ICD to determine whether defibrillator implantation will improve survival in this group of patients.

DINAMIT: Defibrillators in Acute Myocardial Infarction Trial

Because arrhythmic death is common in high-risk survivors of myocardial infarction, this study was devised to examine the effects of defibrillator implantation in patients with a recent myocardial infarction. Patients have to have suffered a myocardial infarction less than 30 days prior to enrollment, an LVEF less than 35% and abnormal heart-rate variability. In addition to receiving medical therapy with aspirin, ACE inhibitors, β-blockers and lipid-lowering agents (statins), patients will be randomized to therapy with or without an ICD.

BEST + ICD Trial: Beta Blocker Strategy Plus ICD

This European trial being conducted at 50 centers is enrolling 1,500 patients who have had myocardial infarctions, in order to determine if there is any difference in survival following EP-guided therapy and defibrillator therapy in contrast to conventional therapy. Criteria for inclusion in the trial are acute myocardial infarction within 5 to 21 days prior to enrollment, treatment with β-blockers, an LVEF less than 35% and a marker of future arrhythmic events such as decreased heart-rate variability, more than 10 PVC/hour, or prolonged QRS duration on filtered and averaged electrocardiograms (late potentials).

MADIT II: Multicenter Automatic Defibrillator Implantation Trial

To address the concerns from MADIT regarding the arm of "conventional therapy," more attention will be given in this trial to avoiding the use of antiarrhythmics and to optimizing the use of ACE inhibitors and β-blockers. Patient eligibility includes surviving a myocardial infarction, LVEF less than 30% and more than 10 PVCs or couplets on Holter monitoring. The aim of this study is to assess whether defibrillator therapy will increase overall survival of patients with coronary artery disease, and at great risk for sudden arrhythmic death.

Secondary Prevention Trials

CASCADE: Cardiac Arrest in Seattle: Conventional versus Amiodarone Study (48)

CASCADE evaluated two different approaches to the management of patients who survived out-of-hospital cardiac arrest and who were at high risk for recurrent cardiac arrest. The empiric use of amiodarone without extensive EP testing or Holter monitoring was compared with standard (Class Ia) antiarrhythmic agents (equinidine, procainamide, disopyramide) guided by EP testing or Holter monitoring. The primary endpoint of the study was total cardiac mortality rate, including sudden arrhythmic death, documented resuscitated out-of-hospital VF, and nonarrhythmic cardiac death. In addition, for patients with an ICD, syncope followed by a shock was designated as the equivalent of a cardiac arrest. In this study, ICD therapy was not randomized and no attempt was made to compare outcomes relating ICDs.

The use of amiodarone in this study significantly reduced the primary endpoints of total cardiac mortality, resuscitated cardiac arrest and syncopal ICD shock. If the endpoints of sustained VT requiring cardioversion and near-syncopal ICD shock were added to the primary endpoints, amiodarone again was associated with a significant reduction. The results of this study indicated that empiric use of amiodarone was more effective in preventing recurrent arrhythmias than conventional antiarrhythmics guided by EP testing. A placebo group was not included in this study, a fact that is clearly important, as learned from the CAST study.

AVID: Antiarrhythmics versus Implantable Defibrillators (49)

With the growing availability of ICDs and the unsatisfactory prevention of death by antiarrhythmics, a study comparing the two modes of therapy was designed. The AVID trial was the first large, randomized, controlled study of the effectiveness of the ICD in the secondary prevention of sudden cardiac death. Patients were eligible for AVID if they had been resuscitated from VF, had sustained VT with syncope, or sustained VT with an LVEF less than 40% and hemodynamic compromise including near-syncope, CHF or angina. Patients were randomized to ICD therapy or antiarrhythmic drugs. Patients receiving drug therapy were given amiodarone or sotalol guided by EP testing or Holter monitoring.

The trial was stopped prematurely when ICD therapy was shown to result in a significant survival advantage compared to antiarrhythmic drug therapy. Based on the results of this study, it has been concluded that a patient who has survived an episode of VF or unstable VT should receive an ICD as first-line therapy. However, even prior to the completion of this study, multiple single-center studies had shown ICD therapy to be superior to antiarrhythmic therapy for life-threatening ventricular arrhythmias. It was pointed out that the AVID trial was too late and to some extent not necessary, given the already established role of the ICD in the secondary prevention of sudden cardiac death (50).

CIDS: Canadian Implantable Defibrillator Study (51)

CIDS was similar to AVID in its design. It compared amiodarone to ICD therapy in patients at high risk for recurrent ventricular tachyarrhythmias. This study was started virtually simultaneously with AVID, but had a longer enrollment and longer follow-up. Inclusion criteria were documented VF, out-of-hospital cardiac arrest requiring defibrillation, documented sustained VT-causing syncope, or documented VT at a rate of at least 150 bpm causing near-syncope or angina, in patients with LVEF of less than 35%. An additional inclusion criterion not included in AVID was unmonitored syncope with subsequent documentation of either spontaneous VT of at least 10 seconds, or sustained (greater than 30 seconds) monomorphic VT induced at EP testing.

The results of this trial showed an overall trend toward a lower mortality and arrhythmic death associated with use of the ICD. The difference, however, was not statistically significant. Several possibilities exist that may help explain the discrepancy between the results of this study and those of AVID: the lack of the use of sotalol, the greater use of β-blockers in the amiodarone arm, and the fact that 5.5% of patients randomized to receive an ICD never actually had the implantation.

Conclusions

Treatment and prevention of sudden arrhythmic death have been a long-standing challenge to clinicians. An immense amount of information has been obtained from studies of antiarrhythmic agents and implantable cardioverter defibrillators. As we better understand the mechanisms underlying arrhythmias and as technology improves, definitive treatment with ablation will become more widely available. Currently, optimum ventricular tachycardia management has evolved to combine ICDs with catheter ablative and drug therapy in an attempt to eliminate or reduce arrhythmia risk. Therapy should not be based on the use of a single strategy; rather, it should be based on the use of combined or hybrid therapy that will provide superior control of arrhythmia and relief of symptoms. The presence of underlying heart disease and left ventricular dysfunction remain important variables that will influence the choice of therapy and its effectiveness.

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Apoptosis:

A Case Where Too Much or Too Little Can Lead to Autoimmunity

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Abstract

Apoptosis is a physiological process of cell death that normally occurs when cells are damaged or no longer needed. One of its major roles is the maintenance of peripheral immune tolerance, by eliminating activated T and B cells beyond the course of an infection, and thus terminating immune responses. When apoptosis becomes dysfunctional, either being "too much" or "too little," a variety of different disease states may be triggered. For example, insufficient apoptosis of activated immune cells is the basis of the Canale Smith Syndrome /ALPS, whereas excessive apoptosis of β islet cells of the pancreas is involved in the pathogenesis of autoimmune diabetes mellitus. In this review, we explain the fundamental aspects and molecular mechanisms of apoptosis and their relevance to several important human autoimmune diseases.

Key Words: Apoptosis, autoimmunity, diabetes mellitus, Canale-Smith Syndrome/ALPS, acute lymphoproliferative syndrome, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis.

Introduction

APOPTOSIS, OR PROGRAMMED CELL DEATH (PCD), is a normal physiological process occurring in senescent or damaged cells. It is a form of demise that serves to eliminate these cells when they are no longer needed. It plays an important role in embryogenesis and normal tissue homeostasis, and is involved in certain pathological conditions as well, such as malignancy, acquired immunodeficiency syndrome (AIDS), certain neurodegenerative diseases, and in autoimmunity (1). Although apoptosis has become one of the major areas of research today, this naturally occurring form of cell death has been a subject of great interest since 1885, when Flemming (2) provided the first clear description of the process, then called "chromatolysis." The term "apoptosis" (from the Greek for the "falling off" of leaves from a tree) was coined by Kerr and Wyllie in 1972 (3). Further developments in the field, particularly in the last decade, paralleled advances in molecular biology, biochemistry, and genetics.

General Mechanisms

Although "apoptosis" refers to cell death, it has several features distinguishing it from necrotic cell death (Table). In contrast to necrosis, apoptosis follows a stereotypical pattern of morphological and biochemical changes, independently of the initiating event (Fig. 1). This process is characterized by plasma membrane blebbing, cytoplasmic and organelle contraction and shrinkage, nuclear chromatin condensation, and ultimately nonrandom DNA fragmentation of multiples of 180–200 base pairs, which is the hallmark of apoptosis (4). The subsequently generated cellular fragments, or apoptotic bodies, rapidly become ingested, via a receptor-mediated mechanism, by neighboring cells and resident tissue

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TABLE

Cellular Modifications Distinguishing Apoptosis from Necrosis

	Apoptosis	**Necrosis**
Cellular role	Active	Passive
Distribution	Dispersed	Contiguous
Morphology	Decreased volume of the cell	Increased volume of the cell
Cellular membrane	Preserved	Loss of integrity
Induction	Slow (hours)	Rapid (seconds – minutes)
Cell removal	Rapid	Slow
Tissue inflammation	Absent	Present

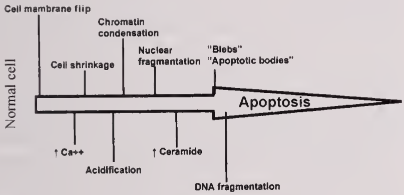

Fig. 1. The process of programmed cell death. Apoptosis, or programmed cell death (PCD), follows a stereotypical pattern of cellular modifications at the morphological and biochemical levels, independently of the initiating event. "Cell membrane flip" refers to the exteriorization of phosphatidylserine during the early stage of PCD.

macrophages. This highly efficient elimination of apoptotic cells occurs rapidly and without tissue inflammation or damage (5).

Although apoptosis is a complex and tightly regulated process, it has been described in very simple organisms and was highly conserved during evolution, suggesting that it has a fundamental physiological role in species survival. The genetic control of apoptosis was first dissected in the nematode *Caenorhabditis elegans*. It was determined that 14 genes (CED 1 – 14) are responsible for the regulation of PCD during the development of *C. elegans*. Two of the gene products (CED-3 and CED-4) are inducers of apoptosis, one (CED-9) inhibits apoptosis, and at least 6 of these genes encode proteins that are required for the engulfment of apoptotic cells (6, 7). The cell death process was further determined to involve four distinct phases: (a) initiation, (b) effector, (c) degradation, and (d) engulfment phase. The initiation phase is triggered by an apoptotic stimulus, and is subject to very intricate regulation. If pro-apoptotic signals override the anti-apoptotic signals, the cell will eventually enter the effector phase, in which the cell becomes "committed" to die. The degradation phase consists of the typical morphological and biochemical changes of PCD, and is beyond regulation (6). The fourth phase involves the receptor-mediated engulfment of apoptotic bodies by phagocytes (8). Defects in the regulation at any of these phases may ultimately result in disease.

Specific Molecular Mechanisms

The various biochemical, molecular and genetic factors modulating apoptosis are complex, and are not yet fully defined. Ultimately, PCD is the net result of the balance between pro- and anti-apoptotic stimuli. The most important regulatory mechanisms of PCD in mammalian cells belong to the following categories: death receptors, caspases, mitochondria, the Bcl-2 family of proto-oncogenes, and certain tumor-suppressor genes.

Death Receptors

Signal transduction after an apoptotic stimulus consists of early events, occurring at the plasma membrane via specific death receptors, and subsequent rapid triggering of a very complex, albeit orderly, intracellular proteolytic cascade of proteases, called "caspases," ultimately resulting in cellular demise within hours (Fig. 2).

Death receptors are located on the surface of certain cells and act as sensors to extracellular apoptotic signals. Such signals are provided by the receptor's specific cognate ligand, which may be membrane-bound or in a soluble form. The ligand-receptor interaction rapidly triggers the recruitment of early signal-transducing molecules. The prototypical death receptors are Fas (CD95; APO-1) and tumor necrosis factor receptor I (TNF-RI) and TNF-RII, and their corresponding ligands are Fas ligand (FasL) and TNF-α, respectively (9) (Fig. 2).

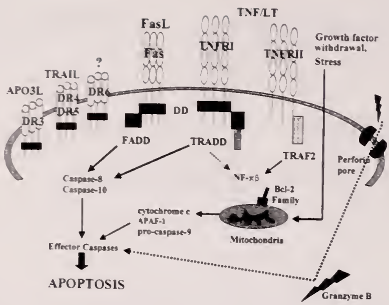

Fig. 2. Cell death pathways. Interactions between cell death receptors and their respective ligands are illustrated, as well as their major intracellular signal transduction pathways. The initial steps occur at the plasma membrane, by the binding of ligand to its cognate receptor, resulting in clustering and recruitment of upstream adaptor molecules. These, in turn, facilitate enzymatic activity of the caspases. Fas/FasL interactions as well as the perforin-mediated internalization of Granzyme B induce PCD by activating caspases. However, tumor necrosis factor α (TNF-α) may induce two distinct outcomes: it may either trigger a death signal through the TNF receptor I (TNF-RI)-associated death domain (TRADD), or stimulate cell proliferation or cytokine transcription through the nuclear factor κβ (NF-κβ) pathway. Mitochondria-mediated apoptosis is induced by cellular stress or growth factor withdrawal, and is usually independent of death receptors in most cell types. Cell death pathways are modulated by the Bcl-2 family of proteins and by other downstream signal transduction pathways (see text). FasL = Fas ligand; LT = lymphotoxin; DD = death domain; FADD = Fas-associated death domain; TRAF2 = TNFR2-associated factor 2; APAF-1 = apoptotic protease activating factor-1.

Signaling by Fas: Fas is expressed on many different cell types, whereas FasL is mainly expressed on T lymphocytes. The major role of the Fas pathway of PCD is the termination of immune responses by causing peripheral deletion of activated mature T lymphocytes. However, it is also involved in preventing inflammation in "immune-privileged" sites, such as the eyes, brain and testes, where FasL is also highly expressed. Another important function of this pathway is the killing of virus-infected or transformed cells (10). Mutations in Fas or FasL are associated with peripheral lymphoid tissue expansion and autoimmune disease (11–13). When FasL binding to Fas takes place, it induces trimerization of the receptor and clustering of its intracellular death domain (9). This leads to recruitment of the cytoplasmic protein FADD (Fas-associated death domain), which subsequently triggers the proteolytic cascade of caspases that ultimately leads to cell death (Fig. 2) (14–16). Each step is under strict regulation by a wide array of molecules (17, 18).

Signaling by TNF-RI: TNF-α is a soluble cytokine produced by activated T lymphocytes and macrophages in response to inflammation and infection (19). After it binds to TNF-RI, events such as receptor trimerization and clustering occur similarly to Fas (20), with intracellular signaling via the recruitment of an adaptor protein, TRADD (TNF receptor-associated death domain) (21), and via the action of several intermediary proteins, finally leading to the activation of transcription factors NF-kB and AP-1 (22). In contrast to Fas, TNF-R-mediated signaling often results in cell activation and proliferation rather than apoptosis, depending on the cell type, the receptor (TNF-RI or II) engaged, and on the interplay of other regulators.

While Fas and TNF receptors are the best characterized, a number of other death receptors have recently been identified, such as death receptor 3 (DR3; also called APO-3/TRAMP/WSL-1/LARD), and death receptors 4 (DR4), 5 (DR5; also called APO-2/TRAIL-R2/TRICK 2/KILLER) and 6 (DR6) (Fig. 2). The role of these new death pathways in immune regulation and in human diseases remains to be determined. For review, see Ashkenazi and Dixit (23).

Caspases

The various death receptors, once triggered, converge upon a common proteolytic, "executioner" pathway, known as the caspase cascade, that ultimately results in the disassembly and degradation of the cell. Caspases belong to the family of cysteine proteases (previously known as ICE [interleukin-1β-converting enzyme] family, now renamed caspases), and are homologous to the CED-3 gene product of *C. elegans* (24). These proteins exist in the cytoplasm as proenzymes with little catalytic activity, but once activated, play important roles in the initiation and effector phases of apoptosis (25). Each caspase consists of a structurally related molecule with a prodomain, and a large (~20 kD) and small (~10kD) subunit that combine to form tetramers after activation (26). The catalytic site thus generated has an unusual substrate specificity for cleavage at Asp-X peptide bonds, and possibly for the substrate's tertiary structure as well. Currently 13 different mammalian caspases have been described, 11 of which have human counterparts (27, 28). They can be classified into different groups according to their susbstrate specificity and function (28–30): (a) upstream enzymes [caspases 8, 9, 10], that serve to initiate and amplify the death signal; (b) CED-3-like [caspases 2, 3, 6, 7], that are involved in the rapid cleavage of structural and vital cellular components, such as PARP (poly(ADP-ribose) polymerase), in DNA repair and supervision of genomic integrity, lamins (important constituents of the nuclear membrane), and certain enzymes involved in mRNA processing and DNA fragmentation (31); and (c) ICE-like [caspases 1, 4, 5 and 13], that may be involved in inflammation rather than death.

Like the clotting and complement cascades, the caspase cascade proceeds in an autocatalytic manner, leading to intense amplification of the initial apoptotic signal. This cascade is regulated by various cofactors (e.g., apoptotic protease activating factor-1; APAF-1, see below), and inhibitors (32–35) at the posttranslational level, by protein-protein interactions (Fig. 2). For review, see Thornberry and Lazebnik (36). Another group of proteases involved in PCD is the family of serine proteases, the most important member being Granzyme B. The Granzyme B-perforin pathway is a critical component of granule exocytosis and the main apoptotic mechanism involved in target-cell PCD induced by cytotoxic T cells and natural killer (NK) cells (Fig. 2). For review, see Greenberg (37).

Mitochondria

Mitochondria are important cellular organelles that are thought to have arisen from an endosymbiotic relationship between eukaryotes and purple bacteria some 2 billion years ago (38). They play a central role in the orchestration of apoptosis, and are located upstream of the caspase cascade (39). Their mechanism of action includes: (a) release of specific proteins, such as cytochrome c, which activates procaspase-9 by binding to APAF-1, a human homologue of CED-4, and thus triggering the caspase cascade (32, 40) (Fig. 2); (b) the disruption of electron transport, which is an early feature of PCD; and (c) modification of cellular oxidation-reduction potential. The initial event leading to these effects occurs at the level of the mitochondrial membrane, with disruption of its outer leaflet, matrix swelling and finally loss of the mitochondrial transmembrane potential (MTP) (41). Several members of the Bcl-2 family reside at the level of the mitochondrial membrane (42), and may possibly function as pores after homo- or heterodimerization, thereby regulating the MTP (39, 43, 44). It has been shown that Bcl-2 directly or indirectly prevents the release of cytochrome c (40, 42). Bax, a death-inducing member of the Bcl-2 family, may act in a caspase-independent manner, presumably by causing damage to the mitochondrial membrane (45). For review, see Green and Reed (46).

Bcl-2 Family of Proto-Oncogenes

Many proto-oncogenes are involved in maintaining cell survival and proliferation. The most important ones are those belonging to the Bcl-2 family. This group of related gene products has survival-promoting (Bcl-2, Bcl-xL, Bag-1, Bik) or death-promoting (Bax, Bak, Bad) capacities (47, 48). Bcl-2 is a functional and structural homolog of CED-9 (6), and encodes a membrane-associated protein located at the mitochondrial and perinuclear membranes (49, 50). Its role is to promote cell survival and proliferation. Translocations of the Bcl-2 gene, leading to overexpression, were first discovered in B cell lymphomas (51–53), and have been associated with poor prognosis of certain cancers (54, 55) as well as with resistance to several chemotherapeutic agents (56–58). For review, see Strasser et al. (1).

Tumor-Suppressor Genes

One of the most important tumor-suppressor genes is p53. The p53 gene product can induce cell death in response to DNA damage (59). Mutations causing its loss of function are associated with many human cancers (60). When p53 becomes activated, two cellular outcomes are possible: apoptosis or cell cycle arrest (61). The role of p53 in cell cycle arrest involves many regulatory proteins, such as the cyclin-dependent kinase (Cdk) inhibitor p21 (62), and the retinoblastoma gene product Rb (63). Mutations in these regulatory proteins are also reported to result in abnormal cellular growth, for example, the development of retinoblastoma in Rb-mutated individuals. The mechanism by which p53 causes PCD is less well defined, but may proceed through the triggering of transcription of specific genes (64). For review, see Evan and Littlewood (65).

Other Apoptosis Modifiers

Aside from the genetically mediated regulators previously mentioned, the cell is also subjected to many other apoptosis modifiers, such as various cytokines (e.g., IL-4, IL-2, IL-10) (66–68), circulating or membrane-bound molecules capable of triggering specific ligand-receptor interactions (e.g., Fas ligand/Fas, TNF-α/TNF-RI), and nitric oxide. Nitric oxide is a potent pro-inflammatory molecule and modulator of the immune system (69–73); it has been implicated in various pathological conditions, such as joint damage related to rheumatoid arthritis (74–77) and osteoarthritis (78–80), as well as in diseases associated with vascular dysfunction (81–84). Various reports have suggested that nitric oxide may play a role in PCD (85–88). A mitochondrial-dependent, pro-apoptotic effect has recently been described. Hortelano et al. showed that nitric oxide increased the mitochondrial membrane potential and chemically modifies cytochrome c, thereby altering its structure and promoting its release from the mitochondria, which subsequently activates caspase-3 (89). An anti-apoptotic effect has also been proposed, where nitric oxide induces the S-nitrosylation of caspases, thereby preventing their activation and promoting resistance to Fas-mediated PCD (90).

Role of Apoptosis in Autoimmune Diseases

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the involvement of multiple organs and the presence of serum autoantibodies against various nuclear and cytoplasmic antigens (91). Although the precise immune disturbance in SLE remains obscure, one hypothesis is that the clearance of apoptotic cells is defective (92–94). Apoptosis is associated with the externalization of phosphatidylserine, which may be important in the generation of antiphospholipid antibodies (95), a common feature of SLE (Fig. 3). Exposure of keratinocytes to ultraviolet irradiation has been shown to cause a redistribution of many nuclear antigens (e.g., RO, La, and nucleosomal DNA) to near the surface of the cell in apoptotic blebs (96, 97). Because lymphocytes from lupus patients have an activated phenotype and undergo accelerated PCD compared with normal individuals *in vitro*, it has been suggested that apoptotic blebs contain modified self-antigens that could be immunogenic. Mevorach et al. recently showed that the immunization of normal mice with a large amount of apoptotic cells resulted in a transient immune response (antiphospholipid and anti-ss-DNA autoantibodies). Taken together, these findings support the indirect evidence that the products of apoptotic cells may drive the humoral autoimmune response in SLE (98) (Fig. 3).

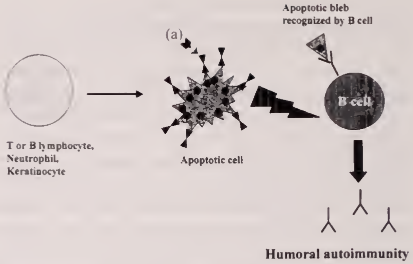
Apoptotic bleb recognized by B cell
(a)
B cell
T or B lymphocyte, Neutrophil, Keratinocyte
Apoptotic cell
Humoral autoimmunity

Fig. 3. Apoptotic cells as a source of immunogens in systemic lupus erythematosus (SLE). The early stages of programmed cell death are associated with the externalization of phosphatidylserine (**a**) and with the redistribution of various modified nuclear antigens (•) such as Ro, La, and nucleosomal DNA, to the surface of the cell within apoptotic blebs. These apoptotic blebs thus contain potential immunogens, which may drive the humoral autoimmunity seen in human SLE (see text).

The mechanisms whereby apoptotic cells are efficiently identified, removed and degraded by adjacent phagocytes in mammalian cells are complex and are not yet fully understood. Several ligands and receptors, such as $\alpha_v\beta_3$ integrin (99) and CD36 (100), have been implicated, and several members of the complement system have recently gained recognition. Deficiencies in the early components of the complement cascade have been shown to predispose humans and mice to lupus-like diseases (101–105), and Mevorach et al. recently reported (106) that serum complement facilitates the uptake of apoptotic cells by phagocytes *in vitro*, in some cases amplified by the presence of C-reactive protein (CRP) (107).

It has also been proposed that defects in certain pro- and anti-apoptotic molecules play a role in lupus-like disease, although most of the evidence is experimental. Most patients with SLE do not have Fas/FasL mutations (108, 109). However, the fact that rare cases with either Fas (110) or FasL (111) mutations exist suggests that defective function of a related death effector could play a role in the pathogenesis of SLE. The levels of soluble Fas (sFas), a secreted form of Fas capable of inhibiting FasL binding *in vitro*, is elevated in the plasma of many patients with SLE. This finding, however, is not specific to SLE, and its role in disease pathogenesis has not yet been elucidated (112, 113). Other regulators of PCD may also be abnormal in human lupus, such as members of the Bcl-2 family (109, 114, 115), T cell costimulatory mechanisms involving CD28 and CTLA4 (116–119), and CD40 (120, 121).

Despite these important advances, further research is needed to understand the precise role of apoptosis in SLE.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with significant morbidity and increased mortality. The hallmark of RA is the presence of joint swelling and destruction due to the inflammation and proliferation of the synovial membrane. At the cellular level, there is remarkable hyperplasia of synoviocytes, mainly of the "fibroblast-like synoviocytes" (FLS), located in the deeper layer of the synovium, which acquire invasive and damaging potential (122). The infiltration of various inflammatory cells into the sublining area results in synovial thickening and pannus formation, which proceeds to destroy adjacent structures (Fig. 4). The local secretion of a number of pro-inflammatory cytokines by the pannus, such as IL-1, IL-6, and TNF-α, leads to the damage of soft tissues around the joint as well as to the prototypical bony erosions of RA. Various reports suggest that defects in the regulation of apoptosis of different cell types is implicated in the pathogenesis of RA (Fig. 4). The RA synovium has an abnormally high proliferative rate, and acquires the unusual ability to invade and destroy cartilage and bone. These observations have led several authors to compare it with tumors (122). This "transformed" phenotype may be explained by the altered expression or function of various anti-apoptotic genes, oncogenes, or tumor suppressors. Among the anti-apoptotic genes studied to date, *Bcl-2*, *Bcl-XL*, and *Survivin* were reported to be overexpressed in RA, FLS and T cells; thus, they may contribute to synovial hyperplasia (123–128). Defects in B-cell apoptosis in RA have also been proposed, to explain the local and especially the systemic autoimmunity observed (129). Somatic mutations in the tumor suppressor gene p53 have also been reported in RA synoviocytes and mononuclear cells, but not in RA skin or in normal or osteoarthritis synovium (130). These mutations occur in what are called "hotspots" (regions in the gene that are often mutated in human neoplasias). Most of the p53 mutations seen in RA synovium are characteristic of oxidative deamination by nitric oxide, suggesting that the nitric oxide generation observed in rheumatoid joints resulting from chronic inflammation may contribute to these somatic genetic modifications (131). The Fas/ FasL pathway of PCD may also be implicated in RA. Fas and FasL are both constitutively expressed in the RA synovium. Both are detected on FLS and mononuclear cells, but the death-inducing FasL is mainly expressed on the invading CD4+ (helper) and CD8+ (cytotoxic) lymphocytes. Although FLS have been shown to be sensitive to Fas-induced cell death by anti-Fas antibodies (132), only a small proportion of FLS actually undergo spontaneous apoptosis in RA joint samples (124). This may be due to the deficient ability of infiltrating FasL-bearing T cells to kill their Fas+ target cells (FLS and mononuclear cells) (133–135). Another possible explanation for the deficient Fas-mediated PCD could be the increased nitric oxide found in RA synovium, as mentioned previously (136). In addition to its pro-inflammatory effects, nitric oxide has recently been implicated in playing a role in Fas-mediated apoptosis, by its ability to S-nitrosylate and thus prevent the activation of caspases (136).

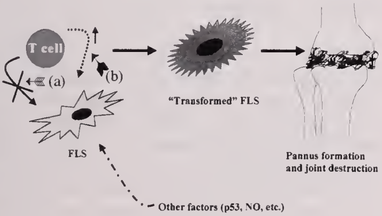

Fig. 4. Schematic representation of the role of defective apoptotic mechanisms underlying the pathophysiology of rheumatoid arthritis (RA). Infiltrating activated T cells in the RA joint relay an insufficient pro-apoptotic signal (**a**), or perhaps an increased anti-apoptotic signal (**b**) to adjacent fibroblast-like synoviocytes (FLS). The net result leads to persistence and enhanced proliferation of the FLS, pannus formation, and joint destruction.

Most significantly, the local enhancement of Fas-mediated cell death has proven to be beneficial, at least in murine models of inflammatory arthritis. The intra-articular administration of anti-Fas monoclonal antibody to transgenic mice resulted in marked and rapid clinical improvement of joint inflammation, with significant increase of apoptosis of synovial fibroblasts and mononuclear cells (137). Similarly, the intraperitoneal injection of anti-Fas into mice with severe combined immune deficiency (SCID: lacking mature T and B lymphocytes) with engrafted human RA synovial tissue was equally beneficial, although more toxic (138, 139). Intra-articular transfer of the FasL gene also succeeded in increasing the rate of apoptosis in FLS by cell-to-cell interaction via the Fas/FasL pathway (140). Similar observations were found with the intra-articular transfer of the FADD gene but with far less damage to chondrocytes (141, 142). Further advances in gene-therapy by selectively targeting proliferating cells in the pannus may prove to be a useful adjunct to the treatment of RA in humans in the future.

Autoimmune Diabetes

Insulin-dependent diabetes mellitus (IDDM) is characterized by the selective destruction of the insulin-producing β cells of the islets of Langerhans of the pancreas. A murine model of IDDM, the nonobese diabetic (NOD) mouse, has permitted the elucidation of many aspects of the pathogenesis underlying human autoimmune diabetes (143). The NOD mouse spontaneously develops IDDM, and the disease progresses through two distinct phases: (a) initially, infiltration of T and B cells, macrophages and dendritic cells occurs, resulting in a peri-insulitis; and (b) at 4–6 months of age, active widespread destruction of the β cells with insulin-resistant hyperglycemia and the development of major clinical manifestations.

The immunopathogenesis of IDDM is complex, and involves the presence of T cells reactive to peptides derived from various self-antigens (insulin, GAD65/67, HSP70), presented by the diabetogenic major histocompatibility complex (MHC) class II allelic products (I-A^{g7} in mice and HLADQβ in humans) (144). In the effector phase, it is thought that both CD4+ and CD8+ T cells act in concert to destroy the pancreatic β cells (Fig. 5). The CD4+ cells are capable of killing target cells directly via the Fas receptor (145) or by promoting effector functions in CD8+ and/or NK cells. Apoptosis of the β cells has been clearly demonstrated in at least one transgenic murine model of IDDM, the NOD-*scid* mouse (146). Many different mechanisms have been proposed to explain the observed PCD in the β pancreatic cells; these mechanisms vary with the different models studied. The major mechanisms implicated include perforin-dependent cytotoxicity, TNF-α (in neonatal, but not in adult NOD mice), and the Fas/FasL pathway of PCD (147–158).

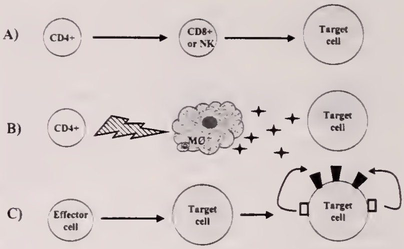

Fig. 5. Models proposed to explain the death of target cells in IDDM and EAE. Th1 CD4+ T cells are responsible for the induction of disease. MHC class II surface expression is required for cells to interact and thereby restrict CD4+ cells. However, MHC class II molecules are not usually expressed on the target cells of these diseases. Three non-exclusive models are presented, by which other cells or mechanisms of cell death may cause tissue destruction. **A)** CD4+ T cells prime CD8+ T cells or NK cells to kill the target cells. **B)** CD4+ T cells interact with the MHC class II-peptide complex of activated macrophages (MØ). This causes killing of the macrophage, thereby releasing substances toxic to the adjacent target cells. **C)** Effector cells induce the upregulation of a death receptor which engages its ligand (expressed on the same cell).

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS), in which myelin and myelin-producing cells (oligodendrocytes; OGD) become the target of an inflammatory response, resulting in fibrosis and ensuing plaque formation. The infiltrating cells responsible for the tissue damage are diverse, and only a small proportion of these cells are autoreactive T cells. Although interest in this entity has increased in the past few years, the identity of the self-antigens and precise molecular mechanisms responsible for tissue injury remain incompletely understood (159). Destruction and cell death of OGD is thought to be the central event in MS, leading to the loss of myelin and to neuronal dysfunction. Although apoptosis is not the sole mechanism involved (160), several studies highlight its role in disease pathogenesis (161, 162). Immunohistochemical analysis of normal brain sections demonstrates that Fas is constitutively expressed on OGD, and low levels of FasL are present on microglia (CNS macrophages) (161). Upregulation of Fas and FasL was noted in samples obtained from chronic active and chronic silent MS disease (160, 162). These observations would be compatible with a straightforward role for either lymphocyte or microglial FasL-mediated killing of OGD in MS. Furthermore, the Fas/FasL pathway of cell death was shown to be involved in the pathogenesis in rodent models of MS. The rodent counterpart of MS, experimental allergic encephalomyelitis (EAE), is also characterized by CNS inflammation and demyelinization, with perivascular inflammatory infiltrates composed mainly of T cells and macrophages in the spinal cord and brain (163). Induction of EAE in susceptible mouse strains carrying the *lpr* or *gld* mutations demonstrated a decrease in severity of disease compared to wild-type controls (164, 165). The amelioration of disease was accompanied by a decrease in apoptotic cell death in EAE lesions of *lpr* mice. These results indicate that the Fas/FasL pathway is important for the progression of clinical disease, most likely by the induction of apoptosis at the site of tissue inflammation (Fig. 5). Although the nature of the cells undergoing apoptosis was not established, these studies suggest that deficiencies in Fas or FasL offer protection from tissue injury, possibly due to decreased killing of OGD. The simplest explanation may be that FasL-bearing T cells are the apoptosis inducers. The target cells remain unknown, but may be MHC class II-bearing macrophages, which have been shown to be required for the expression of EAE (166) and are often apoptotic in tissue lesions of EAE (167). The subsequent release of various proteolytic enzymes and other toxic products (such as TNF-α) from the apoptotic tissue macrophages would thus lead to the destruction of OGD and disease expression (Fig. 5).

Conclusions

Apoptosis, or programmed cell death, is a normal physiological process whereby useless and potentially harmful cells are eliminated in a highly conserved and tightly regulated fashion. The dysfunction of an apoptotic pathway, resulting in either "too much" or "too little" apoptosis, may lead to the development of many different disease states, such as cancer, AIDS, various neurodegenerative and cardiovascular diseases, and autoimmunity, for which the therapeutic options have until now remained limited. Further research into the specific mechanisms involved in the defective apoptosis underlying these and other diseases will ultimately serve to improve therapeutic options.

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Grand Rounds

Osteoporosis:

Trends and Intervention

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Abstract

Osteoporosis is a skeletal disorder in which bone strength is compromised due to loss of bone density and bone quality. It is the leading cause of serious morbidity and functional loss in the elderly. At times, it is difficult for the clinician to distinguish between the disease and normal skeletal aging, but advances in the scientific understanding of the underlying disease process have made management of osteoporosis a preventable disease for the most part. Defining the point at which these age-related skeletal changes require intervention presents a major challenge to researchers and clinicians alike. There are several reasons for these difficulties. There is a long period of bone loss before the onset of clinically apparent disease. Also, although current diagnostic procedures can distinguish those at risk of fracture and those not at risk, there is a large overlap in bone density between persons who experience fractures and those who do not. Research efforts directed at these issues have increased dramatically, as have developing technologies in the measurement and screening of bone mineral density. Ongoing advances in the therapeutic modalities have promoted new methods to treat this disorder.

This review will describe the mechanisms responsible for osteoporosis and the modalities used to screen and diagnose this common disorder. Various therapeutic approaches now in use, and some promising experimental trials, will be discussed.

Key Words: Bisphosphonates, bones, bone remodeling, calcium, DEXA, fracture, estrogen, osteoporosis, postmenopausal osteoporosis.

Introduction

Osteoporosis is characterized by low bone mass as well as microarchitectural deterioration of bone, with a consequent increase in bone fragility and susceptibility to fractures (1). It is the leading cause of serious morbidity and functional loss in the elderly. Progress in the scientific understanding of the underlying disease process has made it, for the most part, a preventable disease. Rapidly developing advances in bone mass measurement and therapeutic modalities have allowed us to recognize and treat this disorder.

Epidemiology of Osteoporosis

Osteoporosis is the most commonly occurring bone disease, and it is anticipated that the prevalence of osteoporosis will increase as the population ages (2). Ten million people in the United States have osteoporosis at the hip and nearly 18 million more have low bone mass at the hip. In the United States alone, the occurrence of osteoporotic fractures is even more striking, approximating 1.5 million per year. One in two women and one in eight men over age 50 will have an osteoporotic fracture (3).

The prevalence of low bone mass increases with increasing age in both men and women, reflecting age-associated bone loss. It is higher for women than men because accelerated bone loss occurs in the immediate postmenopausal period (4). Another difference between men and women is that men achieve a higher peak bone mass than women. Low bone mass is also more prevalent in Caucasians than in blacks (4).

When compared with other common chronic diseases in the United States, the data appear even more dramatic. For white women older than age 65, the incidence of hip fracture is greater than the incidence of stroke, breast

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cancer and diabetes (5). Among other chronic ailments, 28 million are affected with osteopenia and osteoporosis, compared with 52 million and 42 million affected with hypercholesterolemia and hypertension, respectively (6).

The economic toll that osteoporosis places on society is remarkable. The cost of all fractures in the United States is between $35 and 41 billion per year. The cost of all osteoporotic fractures totals between $10 and 15 billion per year. Hip fractures alone total between $4 and 6 billion per year (7). Projected costs for all fractures for the year 2025 are $64 billion (8).

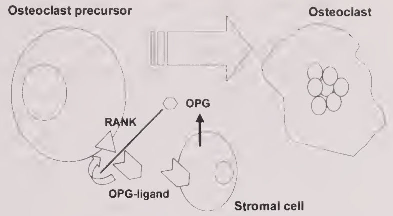

Fig. 1. Discovery of the osteoprotegerin control system. OPG = osteoprotegerin; RANK = receptor activator of nuclear factor-kappa B

Bone Remodeling

In order to understand the pathophysiologic events underlying osteoporosis, it is essential to be aware of the processes involved in normal bone metabolism. Bone undergoes a continuous process of remodeling. Osteoporosis results from defective remodeling. Bone is resorbed by osteoclasts and is formed through the action of osteoblasts. Osteoblasts, formed from pluripotent precursors (which also form adipocytes and fibroblasts), lay down bone matrix (or osteoid) that ultimately becomes mineralized. The cells can either undergo apoptosis, or become buried into the matrix they form and become osteocytes. The latter are transducers of mechanical loading. Osteoblasts express receptors for estrogen and vitamin D in their nucleus, as well as integrin and cytokine receptors on their surface. Endogenous stimulants of osteoblastic activity include fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and transforming growth factor-β (TGF-β).

Osteoclasts, derived from hematopoietic progenitor cells, are giant multinucleated cells found alone or in clusters. Receptor activator of nuclear factor-kappa B (NF-B) ligand (RANKL), or osteoprotegerin-ligand (OPG-L), is now considered to be the single most important cytokine that is both necessary and sufficient for bone formation (Fig. 1) (9). It is expressed on committed preosteoblastic precursors and T lymphocytes. In addition, a variety of other factors modulate osteoclast formation at various stages. These include interleukin-1 (IL-1), IL-3, IL-6, IL-11, tumor necrosis factor (TNF), vitamin D_3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) (10).

To resorb bone, osteoclasts attach to the endosteal bone surface and create a tight seal of close adhesion between their ventral surface and the bone matrix (Fig. 2). Osteoclasts secrete acid through a proton pump system that solublizes the hydroxyapatite crystals and exposes the protein matrix. Digestive enzymes such as cathepsins and metalloproteinases (MMPs) then dissolve the protein matrix and liberate previously deposited growth hormones and collagenases. Thus, the resorptive process includes osteoclast formation from its precursor, polarization with creation of a ruffled border, induction of resorption through acidification and release of enzymes, resulting in the release of molecules from the matrix, and finally apoptosis of the osteoclast.

Once resorption is completed, the resorptive cavity becomes refilled with osteoblasts that initiate formation. In a repeating cycle of events, bone resorption is closely coupled to bone formation. The signal that couples bone resorption with subsequent bone formation is unknown. However, when there is either enhanced osteoclastic activity or decreased osteoblastic activity, each resorption cavity is only partially filled, resulting in net bone loss.

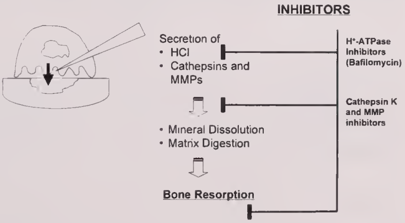

Fig. 2. Resorption by mature osteoclasts. MMP = metalloproteinase.

Defining the Types of Bone Loss

As previously mentioned, bone loss occurs when the processes of formation and resorption become decoupled. There may be absolute osteoclast overactivity (possibly with increased numbers of osteoclasts) in high-turnover osteoporosis, as occurs in postmenopausal osteoporosis (Table 1). Bone remodeling is enhanced, with a disproportionate increase in resorption, resulting in accelerated bone loss. The exact cellular mechanism by which estrogen withdrawal after menopause exerts its effect on osteoclast formation and function is not entirely known. Certain osteoclastogenic and resorptive cytokines, such as IL-6 and M-CSF, are upregulated, leading to enhanced osteoclast formation and activity, which then results in bone loss.

In low-turnover osteoporosis, such as that which occurs with aging, bone formation lags behind resorption; thus, the rate of resorption exceeds that of formation, resulting in net bone loss. There is a primary defect in osteoblastic activity as well as decreased bone formation. The precise cellular details remain unclear. Another hypothesis is that bone loss, even in men, is caused by reductions in the level of estrogen that occur with aging.

Secondary osteoporosis, which is osteoporosis due to conditions other than aging or menopause, may arise from a variety of causes. When patients have unexplained bone loss, laboratory evaluation should be performed to determine if secondary causes may be superimposed on primary bone loss. If laboratory evaluation is negative, a bone biopsy may provide useful information. Common causes of secondary osteoporosis are listed in Table 2.

Predictors of Low Bone Mass and Fractures

Identifying those at risk for osteoporosis and fractures is important in the clinical management of patients. Studies reveal that risk factors for osteoporosis predict fracture, but these risk factors do not predetermine the extent of bone mineral density (11, 12). According to the 1998 National Osteoporosis Foundation (NOF) Guidelines, family history, age, history of fracture, smoking, female sex, Caucasian race, estrogen deficiency, and low body weight are risk factors for the development of osteoporosis (13). Smoking poses a major risk for the development of osteoporosis, increasing the relative incidence of hip fracture by 1.5 – 2.0-fold (14). The same is the case with calcium intake below the recommended daily allowance (15). Other risk factors associated with hip fracture are maternal history of hip fracture, past fracture, particularly after age 50, anticonvulsants, hyperthyroidism and others (Tables 2 and 3).

It is now clear that low bone mass predicts fracture risk (16 – 18). For every standard deviation decrease in bone density measured at any site, the odds ratio for a fracture at any site is 1.6 – 2.4 (19). This relationship holds for both men and women (19). A combination of low bone density plus one or more prior vertebral fractures increases relative risk of fracture by 2.5-fold (19). The risk of fracture increases progressively and exponentially with decreasing bone density.

Diagnosis

The diagnosis of osteoporosis can be made clinically, radiographically or by measurements of bone density (Table 4). As explained earlier, bone mass measurements have now been shown in multiple prospective studies to accurately predict fracture risk (16 – 18). The gold standard for the measurement of bone density is the Dual Energy X-ray Absorptiometry (DEXA).

The World Health Organization (WHO) has defined osteoporosis in terms of bone mineral density in postmenopausal Caucasian women. A bone density measurement of more than 2.5 standard deviations below the mean for young adult women without a history of fractures, using DEXA of the spine, hip, or forearm, con-

TABLE 1
Osteoporosis

Involutional	Postmenopausal	Secondary
Remodeling is normal or decreased	Remodeling is elevated	Etiology-dependent changes in remodeling
Formation < resorption	Formation > resorption	
Osteoblastic defect	Osteoclastic defect	

TABLE 2
Secondary Causes of Osteoporosis

Endocrine	**Gastrointestinal**	**Drugs**	**Genetic & Other**
Hypogonadism	Alcohol	Anticonvulsants	Osteogenesis imperfecta
Cushing's syndrome	Malabsorption	Heparin	Homocystinuria
Hyperthyroidism	Celiac disease	Glucocorticoids	Marfan's syndrome
Type 1 diabetes	Crohn's disease	FK 506	Rheumatoid arthritis
Hyperparathyroidism	Lactase deficiency	Thyroid suppression	Ehler-Danlos syndrome
	Hepatic failure	Vitamin A excess	
Malignancy	Low vitamin D intake	Methotrexate	
Multiple myeloma	Anorexia nervosa	Cyclosporin A	**Renal Disease**
Lymphoma	Gastrectomy	Alcohol	Renal failure
Leukemia	Small bowel resection		RTA
Malignancy- induced PTHrP secretion		**Immobilization**	Idiopathic hypercalciuria
	Lifestyle	Hip fracture	
Mastocytosis	Smoking	Paralysis	

PTHrP = parathyroid hormone-related protein; FK506 = tacrolimus; RTA = renal tubular acidosis

TABLE 3
Risk Factors for Osteoporotic Fractures

Age
Female sex
Caucasian race
Low bone density
Prior fracture after age 50
Hypogonadism
Smoking
Falls
Anticonvulsant therapy
Hyperthyroidism
Alcoholism
Excess dietary protein
Family history
Inactivity
Corticosteroids

stitutes a diagnosis of osteoporosis (20). Note that this criterion identifies approximately 30% of postmenopausal women as having osteoporosis. It approximates an equivalent lifetime risk for spine, hip and forearm of about 17% and lifetime fracture risk for any of the three sites of about 40% (20).

Commonly Used Techniques

Dual Energy X-Ray Absorptiometry

DEXA utilizes a beam of x-ray photons passing through the bone region of interest. This technique measures the sum of cortical and trabecular bone at the mid-radius (95% cortical bone), lumbar spine, femoral neck, total hip and total body, with a precision of approximately 1–3% (21). Radiation exposure is low (1–3 μSv per site) and patient acceptability is high. For the sake of comparison, radiation exposure from a chest x-ray ranges from 50–150 μSv, where 1 Sv (Sievert) equals 100 rem.

Potential uses of bone densitometry include screening of asymptomatic persons to assess their risk of future fracture, diagnostic density measurements of persons with known risk factors for osteopenia, and repeat measurements for purposes of following bone mass changes over time, in response to disease or antiresorptive treatments (22).

Measurement of at least two skeletal sites, usually lumbar spine and hip, is preferable. It is important to recognize falsely elevated bone mineral density on DEXA when interpreting results. Reasons for such artifacts include degenerative joint or disk disease, compression fractures, vascular calcifications, or scoliosis. Use of femoral neck, total hip and forearm as well as a lateral vertebral assessment measurement is usually preferable under these clinical circumstances (21).

TABLE 4
Osteoporosis Diagnosis

Clinical	Radiological	Markers
Height loss	DEXA	OH-proline (hydroxyproline)
Kyphosis	Spinal CT	
X-ray finding	pCT	N- and C- telopeptide
Fracture	µCT	Collagen crosslink peptides
Acute crash syndrome	MRI	
	Ultrasound	

MRI = magnetic resonance imaging
DEXA = dual energy x-ray absorptiometry
spinal CT = spinal computerized tomography
pCT = peripheral computerized tomography
µCT = microcomputerized tomography

DEXA values are reported by comparison to age- and gender-reference groups, with T scores (standard deviations above or below values for young normals) and Z scores (standard deviations above or below age-matched values) (21). A T score more than 2 standard deviations below young normals indicates an increased risk of fracture, and should lead to consideration of antiresorptive therapy to prevent further bone loss, according to the National Osteoporosis Foundation. A Z score of more than 1 – 2 standard deviations below the age-matched mean value should prompt a thorough evaluation for secondary causes of bone loss (Tables 2 and 3).

Quantitative Computed Tomography (QCT)

Vertebral bone densitometry by quantitative computed tomography (QCT) is an attractive alternative to DEXA. This is the only method available that can separately quantitate cortical and trabecular bone, and can potentially detect the signs of bone loss which first occurs in the trabecular skeletal compartment. It allows volumetric bone mineral density (BMD) measurement, and it is useful in degenerative disease in the spine and individuals at extremes for size and weight. However, radiation dose per scan is also substantial and patient acceptability is limited. DEXA is generally preferable to QCT in terms of precision, accuracy, radiation exposure, quality control, and logistics in the clinical radiology setting (21).

Peripheral Measures

Compared to central DEXA, peripheral DEXA and peripheral QCT are performed using smaller, portable units which are easier to operate and emit less radiation. They also require shorter scan times, and decreased cost makes them particularly suitable for screening. Sites measured include the radius, calcaneus and phalanges. Because different normative databases are utilized, these methods are not utilized for serial measurements.

Newer measures of bone strength, such as ultrasound, have been introduced. Currently, only peripheral sites can be measured, including radius, phalanges, calcaneus, and tibia.

Other Modalities

Advances in bone density measurement include lateral vertebral assessment (LVA) which is performed by DEXA as well as magnetic resonance imaging (MRI), and microcomputerized tomography (µCT). These techniques demonstrate actual bone morphology as a measure of bone "quality" through an interpretable digital image. In contrast, DEXA merely provides quantitative information on bone mineral density.

Screening Guidelines

The National Osteoporosis Foundation has recommended densitometry for menopausal women whose decisions regarding estrogen replacement therapy would be influenced by knowledge of bone mass (13). Other recommended indications for densitometry are given in Table 5. These include densitometry in patients with radiographic evidence of osteopenia, patients on chronic glucocorticoids or with other conditions such as asymtomatic primary hyperparathyroidism where knowledge of bone density will influence management (21, 22).

Peripheral measurements of bone density are now being used more frequently for screening. They are useful for screening because of

TABLE 5

1998 National Osteoporosis Foundation (NOF) Recommendations for BMD Testing

1. All postmenopausal women under age 65 who have one or more additional risk factors for osteoporosis (besides menopause).
2. All women age 65 and older regardless of additional risk factors.
3. Postmenopausal women who present with fractures.
4. Women who are considering therapy for osteoporosis, if BMD testing would facilitate the decision.
5. Women who have been on hormone replacement therapy for prolonged periods.

Physician Guidelines to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 1998 and 2000. A copy may be obtained from the National Osteoporosis Foundation, 1232 22nd Street NW, Washington, DC 20037-1292 or <www.nof.org/physguide/indep.htm>

their low cost, as well as their lack of ionizing radiation and their portability. However, results are difficult to interpret, because different normative databases are utilized and T scores do not correspond to the WHO criteria applicable to central DEXA measurements.

Serial Measurements to Assess Bone Loss Rates

Serial densitometries are helpful in determining whether patients need treatment if they have normal baseline bone mass but might otherwise be at risk for rapid loss, as in the immediate postmenopausal period or with the initiation of glucocorticoid therapy. Similarly, assessment of effectiveness of therapy in persons undergoing treatment may benefit from information on bone mass changes over time.

Currently, the only serial measurements that have been substantiated are the ones utilizing DEXA. At present, the available methods are sufficiently precise for measurement of bone mass changes if multiple measurements are taken or expected changes in bone mass are large. For patients undergoing treatments that are expected to produce large (>10%) losses or gains of bone mineral density, serial measurements may help identify nonresponders or patients requiring a change in therapy. Serial measurements over relatively short intervals are not useful in assessing bone mass response to preventive measures such as estrogen replacement, because expected rates of change are small by comparison with the precision variability of the technique.

Biochemical Markers of Bone Turnover

Biochemical markers of bone turnover are a useful adjunct in the management of osteoporosis. High bone turnover, which can be measured by biochemical markers, is an independent predictor of increased fracture risk (23–27). Biochemical markers are useful in assessing rapid bone loss as well as risk of fracture, and in monitoring therapy (28). Common markers of bone formation available for clinical use include alkaline phosphatase, bone-specific alkaline phosphatase and osteocalcin. Resorption markers include pyridinoline, hydroxyproline, deoxypyridinoline, and N- and C-telopeptides. The latter are collagen breakdown products that enter the circulation following bone resorption. Their clinical usefulness in individual patients needs to be determined (28).

Prevention and Treatment of Osteoporosis

Osteoporosis therapy ideally should be aimed at the underlying type of osteoporosis, i.e., involutional, postmenopausal or from secondary causes. The majority of agents available today are antiresorptives that exert the most beneficial effect in those types of osteoporosis with a high rate of bone turnover. See Table 6 for a complete listing of treatment modalities.

Calcium

Multiple placebo-controlled studies (29, 30) have demonstrated the importance of adequate calcium intake for both primary and secondary prevention of osteoporosis. Chronic deficiency inevitably leads to skeletal demineralization

TABLE 6

Osteoporosis Therapy

Decrease Resorption	Enhance Formation
Estrogen and SERMs	Parathyroid hormone
Bisphosphonates	Vitamin D analogues
Calcitonins	Fluoride
New osteoclast-inhibitory agents	New osteoblast-stimulatory agents
	Exercise

SERMs = selective estrogen receptor modulators and enhanced fracture risk (29). The effects of calcium supplementation are maximized in patients in whom baseline intake is low, especially in the elderly (29). Premenopausal and menopausal women, as well as middle-aged and older men and frail female nursing home residents, respond to calcium supplementation with small to modest increases in bone mineral density (30–34). Women in early menopause, presumably because of the dominant effect of gonadal hormone loss, do not show such an effect (29, 30). These data suggest that the use of calcium and vitamin D supplementation should be routine, but must be combined with antiresorptives or bone-forming therapies.

The 1994 Consensus Development Conference on Optimal Calcium Intake advised that the recommended daily allowance (RDA) for calcium be increased in most age groups, particularly in childhood and in adolescence, when 40% of total adult bone mineral is formed. Total, i.e., diet plus supplemental, intakes of 1.5–2.0 g of 'elemental' calcium per day are recommended for postmenopausal women (34), although intake must be individualized.

Exercise

It is evident from multiple studies that immobility and disuse leads to accelerated bone loss. Active individuals have higher bone mass than inactive individuals (35), as has been shown in several cross-sectional studies. Correlations have been shown between muscle mass and bone density. For example, athletes have higher bone mass in skeletal regions of greatest exertion, and some prospective controlled studies in menopausal women have demonstrated increases in bone mass, total body calcium, and improved calcium balance in the exercising groups (35, 36). It is also clear that exercise is less critical than gonadal hormone sufficiency in the prevention of bone loss. Excess weight loss in premenopausal female marathoners leads to amenorrhea, bone loss, and fractures (37).

Questions regarding timing, age at onset, frequency, duration, and type of exercise most beneficial to maintaining bone remain to be answered. Many have proposed that the principal benefit of exercise in reducing fracture risk is its enhancement of muscle strength, balance and coordination, and an associated reduction in the risk of falls (38). General recommendations for exercising include: 30 minutes per day, 5–6 days per week; maintenance of a high level of activities of daily living; and adaptation according to the individual's age, lifestyle, strength and agility. Exercise protocols must be individualized for patients and must be appropriate for their bone density.

Estrogen

At the cellular level, estrogens bind to nuclear receptors present in both osteoblasts and osteoclasts (39–43). Estrogen acts on osteoblasts to produce a spectrum of different effects, including enhanced pro-collagen production, and increased alkaline phosphatase expression (41–45). Estrogen also modulates the synthesis of certain growth factors and cytokines.

Estrogen deficiency causes increased osteoclast formation by enhancing, among other effects, the phosphorylation of the nuclear protein, Egr-1, resulting in an increased production of the osteoclast-forming cytokine, M-CSF, from supporting stromal cells (46). Thus, the availability of estrogen inhibits osteoclast formation. Additionally, estrogen inhibits transcription of the gene for an osteoclast-forming molecule, RANKL (receptor activator for NFκB-ligand) (47). Therefore, in addition to modulating molecules like M-CSF, osteocalcin, osteonectin, and osteopontin, estrogen can directly suppress RANKL-induced osteoclast differentiation and thus bone resorption.

Inhibition of bone resorption by estrogen is evident clinically. When estrogen replacement therapy is initiated early in menopause (i.e., within the first 5 years) and continued for at least 10 years, hip fracture incidence is reduced by 50% (48–52), and significant reductions in distal radial and vertebral fracture also occur. Hormone therapy for preventing bone loss should therefore begin as soon after menopause as possible, in order to inhibit this accelerated loss that ensues within years 4 and 6. When estrogen is given during this phase, some patients may in fact gain new bone, as bone formation during this phase of intense remodeling can transiently exceed bone resorption (49). Thereafter, bone mass is stabilized or the rate of loss is slowed until treatment is discontinued, whereupon rapid loss once again begins. Thus, while estrogen therapy should be given indefinitely, theoretically, every year of use delays the onset of clinically important osteopenia, as demonstrated by the reduced hip fracture incidence seen in elderly women previously treated with hormone replacement (49). In women with established bone loss, estrogen replacement has been shown to increase bone mass slightly, by a few percent over a 3-year period (53, 54). Estrogen also has other benefits, a discussion of which is beyond the scope of this review.

Despite the current knowledge of potential benefits of estrogen in inhibiting bone loss, many women discontinue treatment within one year due to side effects such as vaginal bleeding, and more commonly, fears of breast cancer and thrombosis (55, 56). Large-scale, prospective, randomized studies are required to clarify the ultimate effect of menopausal hormone replacement on overall morbidity and mortality, coronary heart disease, breast and uterine cancer, and osteoporotic fracture. Physicians and patients alike must balance the risk of osteoporosis and coronary heart disease against the risk of breast cancer in deciding for or against menopausal hormone replacement.

Selective Estrogen Receptor Modulators

An important advance in osteoporosis treatment is the development of selective estrogen receptor modulators (SERMs) such as raloxifene, tamoxifen, and droloxifene. Raloxifene has been shown to bind with high affinity to estrogen receptors differently than estrogen, SERMs can confer a conformation that enables the receptor to interact with a different second messenger. Thus, raloxifene is an estrogen agonist for bone and lipoproteins, but an estrogen antagonist at the breast and uterus. Its mechanism of action in bone may involve the up-regulation of transforming growth factor β_3 expression, thus inhibiting osteoclast formation and bone resorption (57, 58).

The clinical effects of raloxifene on BMD and antifracture efficacy have been shown by a number of prospective placebo-controlled trials. Studies have demonstrated a BMD increase of 2.4% at the spine and the hip at three years (59) and a significant reduction, about 30–50%, in vertebral fractures (60). Additional benefits of raloxifene include its favorable lipoprotein profile and a 76% reduction in invasive breast cancer (61). Its side effects include venous thromboembolism and lack of relief of postmenopausal vasomotor symptoms. More long-term studies are needed to evaluate hip fracture efficacy as well as possible side effects on the uterus and breast.

Calcitonin

Calcitonin is a 32-amino-acid peptide hormone synthesized and secreted from the C cells of the thyroid. It is a potent inhibitor of osteoclastic bone resorption and acts on a G protein-coupled receptor in the osteoclast. It triggers both cyclic AMP and calcium pathways to cause osteoclast inhibition (62).

Several prospective controlled trials with calcitonin have also documented stabilization of, and in some cases modest short-term increases in, bone mass in osteoporotic patients treated for 5 years or less (63–65). Similar effects have been demonstrated utilizing calcitonin as a preventive treatment for menopausal trabecular bone loss (65, 66). Studies directly evaluating the impact of calcitonin on fracture rate reduction have all shown that rate to be reduced significantly, together with modest increases in BMD (67–70).

Compromised trabecular microarchitecture is an important and independent causal factor in the pathogenesis of vertebral fractures in both men and women (71). It is now emerging that there is a temporal dissociation between reduction in fracture risk, which can occur in 12–18 months, bone markers and long-term effects on BMD. Notably, a benefit in fracture risk occurs before a change in BMD. Recent clinical trials with antiresorptives, such as calcium plus vitamin D, calcitonin, and raloxifene, indicate significant protection from fracture despite only modest increases in BMD. This has led to the belief that by preventing osteoclastic resorption, antiresorptives, such as calcitonin, conserves bone microarchitecture (72).

Bisphosphonates

Bisphosphonates (BPs) are stable analogs of pyrophosphate that inhibit bone resorption. Their main effects include decreased osteoclast progenitor development, decreased osteoclast recruitment, and induction of osteoclast apoptosis, leading to inhibition of bone resorption (73–75).

Alendronate sodium, a second-generation aminobisphosphonate, has been used for the prevention and treatment of postmenopausal osteoporosis, glucocorticoid-induced osteoporosis and male osteoporosis. Clinical trials demonstrated significant reductions in both vertebral and nonvertebral fractures (76), in association with significant gains in bone mineral density (77), including BMD increases of 8.8%

in the spine and 5.9% in the femoral neck. Its use was associated with a 48% decrease in vertebral fractures (78).

A new bisphosphonate, risedronate sodium, which is a potent third generation bisphosphonate, was recently approved by the FDA for the prevention and treatment of postmenopausal osteoporosis, and for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women.

There is an association between alendronate and erosive esophagitis. Patients often discontinue taking this drug if they experience nausea, dyspepsia and other nonspecific gastrointestinal side effects which usually predate the esophagitis. Recent short-term studies reveal similar increases in BMD with once- and twice-weekly dosing of alendronate in order to minimize gastrointestinal side effects and maximize compliance (79, 80). Long-term efficacy studies are needed to document fracture efficacy.

Other Treatments for Osteoporosis

Sodium Fluoride

Fluoride stimulates new bone formation by increasing osteoblastic activity. Bone biopsies demonstrate increased trabecular volume, thickness and osteoid surfaces. Initially, the new bone formed may be poorly mineralized woven bone, but it is eventually replaced by a lamellar bone structure. Prospective, controlled clinical trials have demonstrated linear increases in spine and hip bone mass, but decreased radial cortical bone mass (81, 82). No significant decreases in vertebral fractures rates were observed in these studies, but there was a significant increase in the number of nonvertebral fractures at sites high in cortical bone (81, 82). This suggests that fluoride may cause formation of new trabecular bone, but not of appendicular cortical bone. At this time, the slow-release sodium fluoride formulation is not commercially available in the United States. Because of its substantial side effects, fluoride is best used only in clinical trials.

Parathyroid Hormone

Parathyroid hormone (PTH) acts on osteoblasts to modulate the expression of a variety of growth factors, including IGF-1, TGF-β1 and TGF-β2, as well as certain cytokines (83, 84). The precise mechanism underlying the anabolic effects of PTH on bone is just beginning to be understood. When administered intermittently, at a low dose, PTH stimulates bone formation (Table 7). Several clinical trials have demonstrated increases in bone mass and volume with low, intermittent doses of PTH (85, 86). Promising data obtained from a recent multicenter clinical trial revealed that daily injections of parathyroid hormone (1-34) at doses of 20 µg and 40 µg, compared to placebo, increased the bone mineral density of the spine by 9 and 13 % respectively, and at the femoral neck by 3 and 6 % respectively. The risk of new vertebral fractures was reduced by 65 and 69 percent respectively, as compared with placebo (87). The major drawback of PTH administration is that it must be administered parenterally to achieve the pulsatile increases in the serum necessary to enable bone formation.

Vitamin D and Vitamin D Analogs

Aging is associated with decreases in intestinal calcium absorption, calcitriol levels and responsiveness of the 1- hydroxylase enzyme to parathyroid hormone stimulation. While vitamin D may indirectly stimulate bone resorption, it also enhances gastrointestinal calcium absorption, promotes mineralization, and inhibits PTH-induced bone resorption.

Results from clinical trials of calcitriol (1,25 dihydroxyvitamin D) have been contradictory. Its use has been associated with an increased risk of hypercalcemia and hypercalciuria, necessitating regular monitoring of calcium intake and serum as well as 24-hour urinary excretion of calcium. Pharmacologic doses of vitamin D metabolites, therefore, cannot be recommended routinely. However, the use of physiologic doses of vitamin D (800 IU per day) has demonstrated efficacy in reducing fracture rates in the elderly, and should now be consid-

TABLE 7
New Bone-Forming Agents

Parathyroid hormone analogues
Calcilytics (Ca^{2+} receptor antagonists) Bone morphogenetic proteins
Growth factor and growth factor binding protein modulators (IGF and TGF-β)
Vitamin D analogues
Prostanoids

ered as standard regimen. While new vitamin D analogues, which carry a decreased risk of hypercalcemia, have been introduced, there are no long-term studies evaluating their use in the prevention or treatment of osteoporosis.

HMG-CoA Reductase Inhibitors

Recent animal studies have shown that the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase by the lipid-lowering statins activate osteoclast apoptosis and reduce osteoclast recruitment, as well as promote osteoblastic bone formation. *In vitro* and *in vivo* evidence has led to the findings that aminobisphosphonates inhibit the biosynthetic pathway from mevalonate to cholesterol, resulting in osteoclast apoptosis. Statins act on the same pathway upstream of bisphosphonates in osteoblasts and enhance the expression of bone morphogenic protein-2 (BMP-2), an important osteoblast differentiation agent. It is thought that BMP-2 upregulation mediates the bone-forming effect of statins.

Promising clinical studies have become available. One retrospective trial involving patients with type 2 diabetes mellitus revealed significant increases in BMD at the spine and the hip in those patients treated with lovastatin, pravastatin, or simvastatin compared to controls (88). Other retrospective studies document a decreased fracture risk in those treated with statins (89, 90). Further controlled, prospective clinical trials are necessary to determine the clinical applicability of statins to osteoporosis treatment.

Other Treatment Strategies

Potential development of bone-forming agents includes growth factors (insulin-like growth factors I and II, and transforming growth factor β), parathyroid hormone analogues, and bone morphogenic proteins which mediate their effects through proliferation of osteoblasts and are currently undergoing evaluation for methods of localizing their effects to the skeleton (Tables 7 and 8).

Conclusion

Through advances in the scientific understanding of bone remodeling, new clinical measures of bone mass, and access to more therapeutic modalities, powerful tools are now available to detect and treat osteoporosis, a disease physically disabling and financially draining. More work needs to be done in order to identify potential therapeutic agents that can increase bone formation. New and better techniques are needed to measure bone strength. With ongoing research, osteoporosis should come to be considered a preventable and curable disease.

TABLE 8
New Osteoclast Inhibitory Agents

Small molecule modulators of osteoclastogenic cytokines and their receptors
Ca^{2+} receptor agonists
H^+-ATPase inhibitors
Integrin receptor modulators
Calcitonin receptor mimics
Nitric oxide donors
Osteoprotegerin (OPG)

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Grand Rounds

Atrial Fibrillation:

The Nonpharmacologic Strategy

Johnny Lee, M.D.

Abstract

Pharmacologic treatment has been used for decades for conversion and prevention of recurrent atrial fibrillation (AF). But the use of antiarrhythmic drugs is associated with substantial side effects and mortality in some patients. Accordingly, it is not surprising that nonpharmacologic techniques have been developed for the management of AF, including the use of atrial defibrillators, atrial pacing methods, and several surgical and radiofrequency catheter ablation procedures.

The atrial defibrillator has been found to detect and treat atrial and ventricular arrhythmias appropriately, with successful termination of spontaneous AF through low energy shocks. Although these devices are promising, the factor which limits their widespread use is not safety or efficacy, but patient comfort. Several studies suggest that atrial-based cardiac pacing may have a beneficial effect in decreasing and preventing AF episodes in patients with sick sinus syndrome. Palliative ablative procedures also available for the treatment of atrial fibrillation include AV junctional modification and AV nodal ablation with permanent pacing, the latter technique being associated with improvements in ejection fraction.

Two potentially curative procedures are the surgical MAZE and endocardial catheter ablation. These techniques are based on placing strategically located lesions in the atrium to disrupt the conduction pathway(s). Recent studies have focused on ablative therapies aimed at the area of the pulmonic veins.

The main therapy for maintaining sinus rhythm after conversion is predominantly pharmacologic. Similarly, in the absence of heart block, if conversion to sinus rhythm is not successful, pharmacologic modalities may be required to control ventricular rate. In any case, planning a treatment regimen for the management of AF should include evaluation of the risks inherent in the use of various drugs as well as more invasive strategies.

Key Words: Atrial fibrillation, nonpharmacologic review management, catheter ablation maze.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, with a reported prevalence of 1.9% for patients under 65 years of age, and 5%–6% of patients over age 65(1). The number of hospital admissions in the United States for AF has more than doubled from 1984 to 1994, from 111,000 to 270,000 (1). The morbidity and mortality of this arrhythmia may be attributed primarily to two factors:

- the propensity for thrombus formation with systemic thromboembolism such as stroke;
- the loss of atrial systolic function as a contributor to ventricular filling;

Many patients will become aware of palpitations due to the irregular rapid ventricular rate. To control these symptoms, improve functional capacity, and reduce the risk of embolism, it is common practice to restore sinus rhythm. However, atrial fibrillation may recur within three to six months in at least one half of treated patients (2).

Pharmacologic treatment has been used for decades for cardioversion and prevention of recurrent atrial fibrillation. But the use of antiarrhythmic drugs is associated with substantial side effects and mortality in some patients. Accordingly, it is not surprising that nonpharmacologic techniques have been developed for the management of AF, including external and internal electrical cardioversion, atrial pacing methods (3) to prevent AF, and several surgical (4) or radiofrequency catheter ablation procedures to cure AF (5).

As stated previously, the three therapeutic goals that should be considered for every pa-

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tient with AF are: (a) rate control, (b) maintenance of sinus rhythm, and (c) prevention of thromboembolism. The purpose of this article is to review the current nonpharmacologic strategies for rate control and maintenance of sinus rhythm in the management of AF (Table 1).

Pathophysiology

Electrophysiologic Mechanism of Atrial Fibrillation

Different nonpharmacologic treatment modalities are based on our understanding of the electrophysiology of AF. Data support the view that reentry is the primary mechanism of atrial fibrillation. More recent electrophysiological observations obtained during intracardiac radiofrequency catheter ablation of atrial fibrillation, however, support the ectopic-focus theory (6). These authors reported that they were able to terminate atrial fibrillation by applying discrete energy primarily within the area where the pulmonary veins enter the left atrium. This is important when understanding curative ablative therapy for AF, because these findings suggest that AF may arise from a focal area in the heart.

A key development in our understanding of the mechanism of atrial fibrillation was the multiple wavelet hypothesis of Moe (7). He noted that, "the grossly irregular wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery." Thus, the more wavelets present, the more likely the arrhythmia will continue. The number of wavelets depend on the atrial mass, refractory period, and conduction velocity of various areas of the atria. In essence, a large atrial mass would favor an increase in the number of wavelets and sustained atrial fibrillation when the refractory period was short and conduction delayed.

The mechanism of initiation of atrial fibrillation is not certain in most cases, and is probably multifactorial. If we assume reentry to be the mechanism of atrial fibrillation, initiation requires an area of conduction block and a wavelength of activation short enough to allow the reentrant circuit in the myocardium. The normal aging process and coronary artery disease may result in anatomic changes that enhance homogeneity in conduction and thereby promote the probability of reentry (1).

TABLE 1
Nonpharmacologic Therapies of Atrial Fibrillation

Palliative
- Atrial Defibrillation
- Atrial Pacing
- Endocardial Catheter AV Nodal Modification
- Endocardial Catheter AV Nodal Ablation with Permanent Pacing

Curative
- Surgical MAZE (multiple atrial incisions)
- Endocardial Catheter Ablation
  - Catheter MAZE
  - Ablation of atrial fibrillation foci

Rate versus Rhythm

There are two established treatment strategies. One strategy is to restore and maintain sinus rhythm, and the other strategy is to control the ventricular response rate. In both strategies, adequate anticoagulation with warfarin therapy is important (8).

The potential advantages of suppressing AF and of maintaining sinus rhythm include a more physiologic control of heart rate, prevention of rate-related cardiac chamber dilatation, better exercise tolerance associated with the atrial contribution to cardiac output, and the possibility of reduced thromboembolic risk (9, 10).

The advantages of simply treating AF with optimal ventricular rate control and warfarin therapy include: avoiding potential proarrhythmic risks, including death, of antiarrhythmic drug therapy (11); avoiding other, less serious, adverse reactions to antiarrhythmic drugs; avoiding frequent recurrence of AF with rapid ventricular response; fewer compliance problems; and lower cost (12).

However, there has never been a large clinical trial with a head-to-head comparison of these two treatment strategies. It has always been postulated that since AF is associated with clot formation in the atria and stroke, maintaining sinus rhythm would obviate this risk (8). The AFFIRM trial (12), sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health, addresses long-term treatment of either paroxysmal or persistent AF in patients at risk for systemic embolism or stroke. This study is designed to evaluate whether maintaining normal sinus rhythm or controlling the heart rate alone results in better survival for patients with atrial fibrillation. This trial will provide clinicians with important data to address some very relevant questions concerning the long-term treatment of AF. The focus of this study will not only be on mortality and morbidity, but also on the quality of life and cost effectiveness. The first patient was enrolled in November 1995 and follow-up is planned through April 2001.

Management of Atrial Fibrillation

Pharmacologic Therapy for Conversion and Maintenance of Sinus Rhythm

Patients who undergo a nonpharmacologic strategy for the management of AF probably have been treated with many medications that have either failed or become intolerable. These include quinidine, procainamide, disopyramide, propafenone, sotalol, flecainide, ibutilide, amiodarone and dofetilide (13 – 16). Few large, randomized clinical trials have assessed the efficacy of these agents in maintaining sinus rhythm. In one study, sotalol was just as effective as quinidine (17). Sinus rhythm was maintained in 50 – 60% of patients treated with propafenone, flecainide, or sotalol, often with fewer side effects than with quinidine (18 – 21). Amiodarone is considered by some to be the most effective agent for drug-refractory, symptomatic, recurrent AF, although very few prospective comparative drug data are available. According to recent studies, nearly two-thirds of patients treated remained in sinus rhythm for up to one-year follow-up (15, 16, 22 – 24). Frequent use of amiodarone for AF is limited by its potentially severe and life-threatening side effects, which may be minimized with lower daily doses.

One recent study, the Canadian Trial of Atrial Fibrillation Investigators (25), found that amiodarone was more effective than sotalol or propafenone for the prevention of recurrences of atrial fibrillation. Of the 403 patients in the study, 201 were assigned to a regimen of amiodarone and 202 to one of either sotalol or propafenone. After a mean of 16 months of follow-up, 71 of the patients who were assigned to amiodarone (36%) and 127 of those who were assigned to sotalol or propafenone (64%) had a recurrence of atrial fibrillation ($p<0.001$).

Ibutilide (26) is a class III (Table 2) antiarrhythmic drug, its predominant action being prolongation of the myocardial action potential duration. The mode of action is believed to involve activation of a late inward sodium current and possibly blockade of the rapidly activating component of the cardiac delayed rectifier potassium current (27). A review of 2 placebo-controlled trials involving 439 patients with sustained atrial flutter or AF reported that 33 to 49% of these patient converted to sinus rhythm after intravenous administration of ibutilide, 0.01 to 0.025 mg/kg or a total dose of 1 to 2 mg (28). In another trial involving 300 patients who developed atrial flutter or fibrillation after cardiac surgery, ibutilide, 2 mg, administered intravenously, successfully converted the arrhythmia in 57% of patients. The mean time to conversion was about 30 minutes in these trials (28). In another study, conversion to sinus rhythm occurred in 36 of 50 patients who had not received ibutilide (72%) whereas all 50 patients who had received ibutilide pretreatment

TABLE 2
Classification of Antiarrhythmic Drugs

Class		Action	Channel effect and/or ECG changes
I		Direct membrane action	Blocks fast sodium channels (Phase 0)
	1a	Intermediate inhibition	Prolongs QRS and QT
	1b	Less inhibition	Minimal effect of QRS and QT
	1c	Marked inhibition	Prolongs QRS and QT
II		β-adrenergic blocker	Indir4ect closure of calcium channels (Phase IV); no effect on QRS and QT
III		Prolongation of repolarization	Blocks outward potassium channels (Phase III); prolongs QRS and QT
IV		Calcium channel blocker	Blocks slow inward (AV nodal) calcium channels (Phase II); no effect on QRS and QT

and external cardioversion converted to sinus rhythm (p<0.001) (29). In 3 trials, ibutilide was significantly more effective than racemic sotalol or procainamide in terminating atrial flutter or fibrillation (13, 18, 26). Important side effects which must be monitored include: sustained polymorphic ventricular tachycardia, torsades de pointes, which developed in 1.7%, and non-sustained polymorphic ventricular tachycardia, which occurred in 2.7% of 586 patients treated with ibutilide in clinical trials. The drug has minimal hemodynamic effects and is associated with few noncardiovascular adverse events. Thus, ibutilide is a useful agent for the pharmacological cardioversion within 30 days of recent-onset atrial fibrillation or flutter, provided that adequate steps are taken to monitor for proarrhythmic events.

The Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group (30), found that dofetilide, a novel class III antiarrhythmic drug that selectively inhibits the rapid component of the delayed rectifier potassium current and prolongs the refractory period, was effective in converting atrial fibrillation and preventing its recurrence in patients with congestive heart failure. Of the 190 patients with AF at baseline, 22 patients (12%) had sinus rhythm restored, as compared with only 3 of 201 patients (1%) given placebo. Once sinus rhythm was restored, dofetilide was significantly more effective than placebo in maintaining sinus rhythm (p<0.001). As a pure class III agent, it has no negative inotropic effects, even in patients with markedly impaired left ventricular function (31). Thus, dofetilide is a useful drug to consider in the management of the common combination of heart failure and atrial fibrillation. The risk of developing torsades de pointes is 3.3% (30).

Nonpharmacologic Therapy for Conversion and Maintenance of Sinus Rhythm

Pharmacologic treatment has been used for decades for cardioversion and prevention of recurrent atrial fibrillation but the use of antiarrhythmic drugs is associated with substantial side effects and proarrhythmia in some patients (Table 3). Accordingly, it is not surprising that nonpharmacologic techniques have been developed for the management of AF, including external and internal electrical cardioversion, atrial pacing methods to prevent AF, and several surgical or radiofrequency catheter ablation procedures. The current nonpharmacologic therapies and their mechanisms of action, as well as their potential limitations, are summarized in Table 4.

TABLE 3

Side Effects of Current Antiarrhythmic Therapies in AF

Antiarrhythmic	Side Effects
Class Ia	Proarrhythmic and/or torsades de pointes
Quinidine	Diarrhea, hypotension, cinchonism, torsades de pointes (4.4%)
Procainamide	SLE (20%), hypotension, agranulocytosis
Disopyramide	Anticholinergic effects (29%), hypotension
Class Ic	Proarrhythmic
Flecainide	Significant negative inotrope, neutropenia, ventricular proarrhythmia (5 – 30%)
Propafenone	Nausea, dizziness, cholestatic jaundice, headache, ventricular proarrhythmia (5%)
Class III	Proarrhythmic and/or torsades de pointes
Amiodarone	Hyper-/hypothyroidism, pulmonary fibrosis, corneal deposits, blue-gray skin
Sotalol	Proarrhythmic Torsades de pointes (2.5%)
Ibutilide	Proarrhythmic Torsades de pointes (4.3%)
Dofetilide	Proarrhythmic Torsades de pointes (3.3%)

SLE = systemic lupus erythematosus

Atrial implantable defibrillator. Patients for whom external cardioversion is unsuccessful present a management dilemma and are often considered to have permanent AF. For this small but significant group of patients, internal cardioversion is thought to be of value. The rationale for internal cardiac defibrillation in this setting is to decrease the amount of extracardiac tissue involved in the current path, which maximizes the potential gradient within the atrial tissue and increases the success rate of atrial defibrillation. In recent years there has been a substantial effort to develop a catheter-based lead system for internal atrial defibrillation (32).

Low-energy internal atrial defibrillation has been performed in animals and humans (32). The lowest defibrillation threshold of available transcatheter techniques with an energy of 1.1 to 8.9 joules (J) was found in the region between the coronary sinus and the right atrium.

TABLE 4

Mechanisms and Limitations of the Current Nonpharmacologic Therapies for AF

Nonpharmacologic Method	Mechanism	Limitations
Atrial Defibrillator	Internal defibrillation (1.1 – 8.5 J)	Painful and intolerable
Atrial Pacing	Biatrial synchronous pacing	Sick sinus syndrome patients only
Palliative Catheter Ablation	Modification or ablation of the atrioventricular node	Requires permanent pacemaker implantation
Surgical Maze	Multiple linear atrial incisions	Prolonged cardiac ischemic time during procedure
Curative Catheter Ablation	Multiple linear atrial lesions by radiofrequency energy or focal lesions at the pulmonic veins	High recurrence and pulmonic vein stenosis

Low-energy transcatheter atrial defibrillation is safe, with few complications and high success rates. Some of the reported complications have been: subclavian venous thrombosis, pericardial effusion and lead dislodgement (33–35). Unfortunately, even with the low energies used, the shocks are often painful and intolerable to the patient (33). This reduces the clinical utility of the current implantable atrial defibrillator models.

Both single-chamber and dual-chamber defibrillating devices are available. The METRIX device or Atrioverter (InControl, Redmond, WA) (35), was the first implantable atrial defibrillator developed; it entered the clinical arena in 1995, weighing 82 g. This unit has sensing and defibrillation capability in the atrium and sensing and pacing capability in the ventricle. Its maximal output for atrial shocks is 6.4 J. In the METRIX clinical study of patients with AF (36), a total of 290 patients had the device implanted. Every patient had failed 4 antiarrhythmic drugs. Their average ejection fraction was 50%. In the clinical trial, a total of 614 episodes of AF were treated with 1,497 shocks, with 2.4 shocks per episode. There was a 93% conversion rate to sinus rhythm. In a more recent multicenter study, Wellens et al. (35) present their first experience with the Atrioverter. With 51 patients, the overall success rate of the device for cardioversion to stable sinus rhythm with or without additional drugs was 86%.

Another unit, the JEWEL AF 28 (36) (Medtronic, Minneapolis, MN), is a similar device, weighing 93 g and having dual-chamber sensing and pacing as well as defibrillation capability in both the atrium and ventricle. Its maximum output is 27 J. This unit has wide flexibility as a ventricular defibrillator capable of atrial defibrillation as well. It has been found to detect and treat atrial and ventricular arrhythmias appropriately. Termination of episodes of spontaneous atrial flutter and AF is achieved by pacing.

Although these devices are promising, the factor which limits their widespread use is not safety or efficacy, but patient comfort. Any defibrillating shock greater than 1 J is uncomfortable for most patients. Mean defibrillation threshold in the METRIX experience was approximately 3 J. The atrial defibrillator needs to err on the side of not giving inappropriate shocks for a nonlethal rhythm, in contrast to ventricular defibrillators, which must not miss lethal ventricular arrhythmias (32).

Atrial pacing. Cardiac pacing in atrial fibrillation has been prescribed in the past for patients with a slow ventricular response. Several studies suggest that atrial-based cardiac pacing may be beneficial in decreasing AF episodes. Two pacing modalities have been studied, antibradycardia and multi-site pacing.

Pacing to prevent atrial fibrillation in sick sinus syndrome. Patients with sick sinus syndrome commonly develop supraventricular tachycardias, predominantly atrial fibrillation (tachycardia-bradycardia syndrome). There has been much debate on whether atrial-based or ventricular-based pacing is preferred for sick sinus syndrome patients. Retrospective studies have evaluated the incidence of atrial fibrillation in patients with single-chamber ventricular pacing versus atrial pacing or dual chamber pacing. Results indicated that the incidence of atrial fibrillation was reduced in patients who received atrial-based pacing (37). By inhibiting or triggering pacing in patients in whom VVI (ventricle paced, ventricle sensed and inhibited response to sensing) was used, the annual incidence of atrial fibrillation was 5–15% versus 1–3% in patients in whom either AAI (atria paced, atria sensed and inhibited response to sensing) or DDD (dual-chamber paced, dual-chamber sensed) was employed. Decreased incidence of stroke and congestive heart failure, with a trend to lower mortality was noted. This is probably due to restoration of synchronous contraction of the atria.

A randomized prospective study compared AAI to VVI pacing (38). The investigation included 225 consecutive patients with the sick sinus syndrome, randomized to atrial or ventricular pacing and followed for 5 years. The results show a trend to an increased incidence of atrial fibrillation and stroke in patients receiving VVI pacing. The incidence of atrial fibrillation was 14% in the AAI group and 23% in the VVI group (p=0.12). Thromboembolic events occurred in 17.4% of the VVI group but in only 5.5% of the AAI group (p=0.0083). There was no difference in mortality or development of congestive heart failure. In summary, the data support use of atrial-based pacing in patients with sick sinus syndrome.

Multisite pacing. Intra-atrial conduction block results in a very delayed activation of the left atrium, and may be associated with an increased incidence of atrial tachyarrhythmias. In a preliminary study of 28 patients, permanent atrial resynchronization resulting from simultaneous right atrial and coronary sinus pacing corrected the intra-atrial dyssynchrony expressed by reduction of P-wave duration (39). In 21 patients, this biatrial synchronous pacing prevented arrhythmia recurrences during follow-up of 34±15 months (39). Use of dual-site atrial pacing, in the high right atrium and coronary sinus os, was evaluated in a prospective study in fifteen patients with paroxysmal atrial fibrillation who had bradyarrhythmias warranting permanent pacemaker implantation (40). Dual-site atrial pacing with an optimal drug regimen resulted in a marked decline in atrial fibrillation recurrences. Multisite atrial pacing is feasible and safe, and appears to be effective. Further research may demonstrate that this pacing modality should be considered as a primary mode of treatment to prevent AF.

Palliative catheter ablation. The palliative ablative procedures that are available for the treatment of atrial fibrillation are AV junctional ablation and AV nodal modification. The goal of AV junctional ablation is to interrupt completely the AV conduction with a lesion placed in the immediate area of the AV node. In most cases after AV junctional ablation, the patient has a slow but tolerable junctional escape rhythm originating from the low AV node or high His bundle region immediately distal to the site of ablation. This escape rhythm is usually adequate to prevent hemodynamic embarrassment, but not adequate to maintain a normal heart rate at rest or with activity. Therefore, permanent ventricular pacemaker implantation is always required.

AV junctional ablation and permanent pacing. In some patients with permanent atrial fibrillation, drug therapy to control ventricular response is either ineffective or not tolerated. An alternative approach is endocardial catheter ablation of the AV junction that results in complete heart block (41). These patients require a permanent pacemaker. Improvement in exercise tolerance (41) and quality of life (42) has been demonstrated with this procedure.

The technical success rate of AV junctional ablation is excellent, ranging from 95–100%, when performed by experienced operators (43). In appropriately selected patients, marked improvement in symptoms can be anticipated, with decreases in palpitations, effort dyspnea and exertional intolerance. Improvements in exercise time and ventricular function have been measured 3 months after ablation. In one study of patients with atrial fibrillation and reduced left ventricular function, 90% of patients had improvement in their left ventricular ejection fractions and a decrease in left ventricular and atrial dimensions (43). Another recent, large, multicenter trial, the Ablate and Pace Trial (APT) (44), treated 157 patients with ablation-paced therapy. In 14 of 46 patients, there was a dramatic increase in ejection fraction, from a mean ejection fraction of 33 to 61% at 3 months (41, 44). Cardiac output was not measured. Other studies have also seen significant improvements in ejection fraction from 43 to 54% post-ablation (45), as well as improvements in treadmill exercise performance (41).

AV node modification. Total AV junction ablation requires pacemaker implantation. Another technique for slowing the ventricular rate during AF without creating irreversible heart block has been developed. The method involves modifying AV node conduction to prevent rapid ventricular rates. Several studies have demonstrated the feasibility of modifying AV node function without creating AV block (46, 47). AV node modification is effective in about 70% of patients. Inadvertent AV block may occur in 16% to 21% of patients, and one episode of sudden death has been reported (46).

The goals of AV nodal modification procedures are to damage but not destroy all AV nodal conduction. In the ideal case, the patient will have adequate basal rates, but the rapid acceleration of the ventricular rate with exercise or stress will be prevented. It is important to note that the atria will continue to fibrillate after AV junctional ablation or modification, despite excellent heart-rate control and resolution of the patient's symptoms. Therefore, the patient is still at risk for stroke, and ongoing treatment with anticoagulation is recommended.

The acute success rate of AV nodal modification procedures is approximately 70% (48, 49). Because the injury to the AV node is nonspecific, the frequency of complete heart block with this procedure ranges from 0–21% (48, 49). Clinical outcome has been favorable in patients with an initial successful response over short-term follow-up. Even with successful heart-rate control, patients treated with AV nodal modification will continue to have an irregular ventricular response to their atrial fibrillation and may have persisting symptomatic palpitations. For this reason, AV junctional ablation and pacemaker implantation is the procedure of choice in most cases.

Surgery. Several surgical approaches have been used to treat patients with AF (4, 50). The most popular is the MAZE (4) operation, where multiple atrial incisions are made to channel sinus impulses through a path, or "maze," to reach the AV node. This prevents a large area of contiguous atrial tissue from sustaining AF while maintaining atrial contractility. The long-term effects of this technique have been favorable and effective (4). In a study of 178 patients, 32 patients underwent the Maze-I procedure, 15 underwent the Maze-II procedure, and 118 underwent the Maze-III procedure. During the follow-up (3 months to 8 years), patients were accessed for recurrence of atrial flutter and atrial fibrillation. Ninety-three percent (93%) of the patients were arrhythmia free. Another study by Kosakai et al. (50), had a success rate of 84% with a modified MAZE procedure.

The most successful is the Maze III procedure (43). It is a complex operation, which involves a number of predesignated incisions in both atria, along with cryolesions applied at certain points. The objective is to interrupt micro re-entrant circuits in the atria while ensuring that the SA node is able to generate and propagate the sinus impulse through both atria. This procedure requires prolonged myocardial ischemia and cardiopulmonary bypass, which detracts from its utility despite its success. Results from surgical approaches suggest that large areas of the atria must be isolated electrically to prevent AF. Efforts are underway to replicate the MAZE incisions using radiofrequency energy to produce equally effective intramural ablation more quickly and with less risk. Catheters capable of creating contiguous, multiple, transmural, linear lesions also are being developed to facilitate rapid ablation of AF of the atria. Their introduction will significantly shorten the duration of the MAZE procedure (43).

Early results have been promising, but long-term follow-up of substantial numbers of patients with a variety of causes of AF is lacking. Many patients may require implantation of a permanent pacemaker after the MAZE procedure.

Curative catheter ablation. The MAZE procedure has been the primary surgical treatment for atrial fibrillation (4). A procedure in which linear lesions create endocardial compartmentalization and a maze-like result has been developed using radiofrequency catheter ablation energy (5).

Since the size of the reentrant circuit is determined by the conduction velocity and refractoriness of the tissue (51), the imposition of conduction blocks at critical anatomical sites may inhibit the propagation of the fibrillatory waves. This was the theoretical basis of the MAZE procedure (52). It was hypothesized that similar, long, linear atrial lesions could be achieved by catheter ablation.

Experimental studies have demonstrated that multiple linear lesions in the right and left atria can prolong atrial fibrillation cycle length and, ultimately, terminate this ongoing arrhythmia. It was also demonstrated that lesion continuity was not necessary for successful termination and prevention of reinitiation of the atrial fibrillation (52). The first cases of atrial fibrillation ablation in patients employed a technique of dragging a typical 4 mm tip ablation electrode along the atrial wall during ongoing radiofrequency energy delivery. Chronic atrial fibrillation could be successfully terminated in the majority of cases, but over half of the patients had arrhythmia recurrence and required at least a second ablation session (43).

In a study of 224 patients (5) with paroxysmal AF, 45 patients received a linear right-atrial ablation, 44 patients received right-atrial, septal, and left-atrial ablations and 135 patients received a focal ablation in the pulmonic veins. The catheter was introduced into the left atrium transseptally. The right atrial ablation cure rate was 15% and the combined bi-atrial cure rate was 57%. The pulmonary vein experience is by far the most interesting. The success rate varied between 20% (if only 4 pulmonic veins were involved) and 89% (if 1 pulmonic veins was involved). The overall success rate was 69% (5). Right atrial catheter ablation failed to terminate atrial fibrillation. In contrast, left atrial ablation, either alone or after right atrial ablation, was found to be highly effective in the termination of chronic atrial fibrillation (in 28 of 30 patients, sinus rhythm was restored) (5). In addition, pulmonary vein ablation has shown promising results in the termination of paroxysmal AF (5, 6).

A new approach to catheter ablation of atrial fibrillation. A new approach to catheter ablation of AF is now under investigation and is claimed to have an advantage over the radiofrequency techniques currently used. This catheter technique uses ultrasound energy in a through-the-balloon procedure developed at and licensed to Atrionix (Palo Alto, CA), and is already in clinical trials in both the U.S. and Europe (53).

Ultrasound through a balloon. This new approach to ablation of AF focuses on the pulmonary veins and uses sound waves to destroy errant heart tissue. This method, also known as anatomic pulmonary vein isolation with through-the-balloon ultrasound ablation (TTB-USA) (53), was invented by Lesh. It is based on the principle that a circumferential lesion at the base of one or more pulmonary veins would electrically isolate the veins from the atrium. Therefore, the electrical activity from within those veins would be unable to reach the body of the atrium and thus could not trigger or potentiate AF.

To perform the circumferential lesion, Lesh and colleagues developed a novel over-the-wire catheter design that integrates a cylindrical ultrasound transducer within a saline-filled balloon, which is introduced transseptally. The balloon is placed at the mouth of one or more of the pulmonary veins, allowing ultrasound ablation of a narrow ring of tissue in the area where the vein meets the atrium (53).

Summary

The three therapeutic goals that should be considered for every patient with AF are: (a) rate control, (b) maintenance of sinus rhythm, and (c) prevention of thromboembolism. It is unclear at this moment whether a strategy of primarily rate control or maintenance of sinus rhythm is superior.

The limited efficacy and proarrhythmic risks of antiarrhythmic drug therapies for atrial fibrillation have led to the development of nonpharmacologic therapeutic approaches. The interventional therapies that are currently being examined include prophylactic atrial pacing, atrial defibrillator therapy, atrial surgery, and catheter ablation of atrial fibrillation. All of these strategies, including the MAZE surgical procedure, are directed either at prevention or termination of atrial fibrillation, whereas the presently established nonpharmacologic options of atrioventricular (AV) nodal ablation followed by pacemaker implantation or AV nodal modification only offer ventricular rate control.

Conclusion

When planning treatment for AF, different pharmacologic therapies should be considered along with nonpharmacologic strategies. Pathophysiology of AF is probably multi-factorial, i.e., ectopic focus (pulmonary veins) and reentry (the atria). Evaluating the factors involved in any patient with acute or recurrent paroxysmal AF, or chronic AF, may enhance the success of the options: using various drugs alone, nonpharmacologic procedures, or a combination of both.

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Research Seminar

Aquaporin Water Channels and Brain Edema

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Abstract

Brain edema accounts for much of the morbidity and mortality associated with common neurological conditions such as head trauma, brain tumors, stroke and liver failure. Treatment options are limited to osmotic agents such as mannitol, surgical decompression, and other maneuvers, none of which correct the molecular-level mechanisms responsible for brain swelling. Recent data suggest that aquaporin (AQP) water-transporting proteins may provide a key route for water movement in the brain. AQP1 is expressed in choroid plexus and probably facilitates cerebrospinal fluid secretion. AQP4 is expressed in astrocyte foot processes near capillaries and in ependymal cells lining the ventricles — key sites for water movement between the cellular, vascular, and ventricular compartments. AQP4 expression is markedly altered in experimental models of brain injury and swelling, and transgenic mice lacking AQP4 are partially protected from brain swelling in response to acute hyponatremia and ischemic stroke. Aquaporins and regulators of brain aquaporin expression are thus potential targets for discovery of compounds for treatment of brain swelling.

Key Words: Brain swelling, cytotoxic edema, vasogenic edema, water transport, water permeability, stroke, tumor, encephalopathy, transgenic mice.

Brain Edema as a Clinical Problem

EDEMA IS DERIVED FROM the Greek *οίδημα* for "swelling." Brain edema is produced when fluid accumulates in the brain parenchyma (Fig. 1). It is seen in primary brain pathologies such as stroke, head injury, brain tumor, and brain abscess. Brain edema is also seen in globally important systemic infections that primarily involve the brain (such as childhood cerebral malaria, African trypanosomiasis and meningitis) and in conditions that effect the brain indirectly (e.g., sepsis, hyponatremia, and liver and kidney failure) (1 – 6). Brain swelling increases intracranial pressure (ICP), which impairs vas-

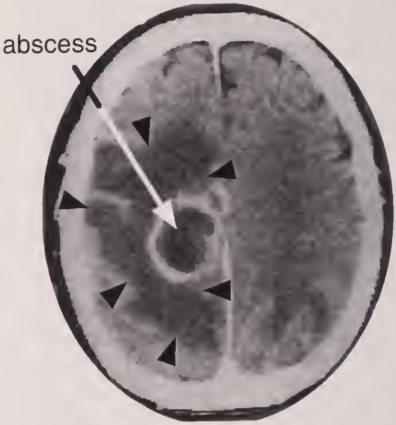

Fig 1. Contrast-enhanced head CT scan of a patient with an abscess in the right hemisphere. The abscess is surrounded by a hypodense area (black arrows) indicating edematous brain. Note that the edema (vasogenic) predominantly involves the white matter.

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cular perfusion and can lead to brain ischemia, herniation and death.

Treatment options for brain edema include osmotic diuretics, corticosteroids, maintenance of normocapnia, surgical excision of the underlying lesion, barbiturate coma, hypothermia and decompressive craniectomy. For critically ill patents, invasive monitoring of ICP and cerebral perfusion pressure is done to optimize therapy (7). However, many of these therapies to reduce brain swelling were introduced early in the 20th century and their efficacy is limited (8, 9). The paucity of effective drugs to be used against brain edema reflects, among other things, the incomplete understanding of the molecular mechanisms involved in the formation and resolution of brain edema.

Mechanisms of Edema

The volume of the intracranial cavity containing the brain parenchyma, the cerebrospinal fluid and blood is about 1200–1400 mL in humans (Fig. 2A). Exchange of fluid between these compartments occurs at the blood-brain barrier, ventricular ependyma, choroid plexus, and arachnoid granulations. In addition, up to 30 mL of water is produced daily from glucose metabolism. Osmotic gradients and hydrostatic pressure differences are the forces that drive water movement between the intracellular, interstitial, ventricular cerebrospinal fluid (CSF) and vascular (blood) compartments in the brain (Fig. 2A).

Brain edema is the accumulation of water in the brain parenchyma. Because the adult skull is mechanically rigid, an increase in brain parenchymal volume results in displacement of fluid from the low-pressure (~10 mm Hg in man) CSF, low-pressure (~10 mm Hg) venous, and high-pressure (~105 mm Hg, mean arterial pressure) arterial compartments (Monro-Kellie doctrine). The ability of the intracranial contents to resist a rise in intracranial pressure (ICP) as the brain parenchyma volume increases is largely due to the capacity of the CSF and venous compartments to contract (Fig. 2B).

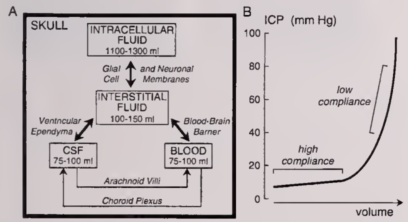

Fig 2. A. Schematic of intracranial fluid compartments (in boxes) and the directions of water movement between them (arrows). Arrows are labeled with barriers separating indicated compartments. B. Intracranial pressure (ICP) as a function of the volume of an expanding intracranial lesion. As the lesion expands there are compensatory mechanisms (reduction in CSF and cerebral blood volumes) that maintain a normal ICP (high compliance). Further volume expansion produces large increases in ICP (low compliance).

Igor Klatzo classified brain edema as vasogenic or cytotoxic (10). Vasogenic edema occurs when the blood-brain barrier becomes leaky, permitting the entry of plasma fluid into the brain parenchyma (3, 5). Brain tumor edema is an example of vasogenic edema. Vasogenic edema fluid is extracellular and accumulates primarily in white matter, because resistance to fluid flow is less in white than in grey matter. Tight junctions in microvascular endothelia open in vasogenic edema. The recent discovery of tight-junction-associated proteins (occludin, claudin, JAM, ZO-1, ZO-2, ZO-3) may provide some clues to the molecular mechanisms involved in the breakdown of the blood-brain barrier. For example, glioblastomas and metastatic brain carcinomas, which can be associated with marked brain edema, show abnormal expression of endothelial cell occludin (11), claudin-1 (12), claudin-5 (12) and ZO-1 (13).

Cytotoxic edema consists mainly of intracellular fluid accumulation that occurs during water intoxication and anoxia-generating conditions such as stroke, trauma and hypoxia. Cytotoxic edema also results as a direct consequence of infections such as cerebral malaria, which causes microvascular obstruction due to adherence of *Plasmodium falciparum*-infected erythrocytes to cerebral capillaries (1, 2). It is believed that the astrocyte is the major cell type showing swelling after ischemia and trauma (14). Astrocyte swelling may be an important early event predisposing the brain to further damage, because of the impairment of protective homeostatic mechanisms. Astrocytes *in vitro* show regulatory volume decrease in response to hypoosmotic media, with loss of intracellular ions (mainly K^+ and Cl^-) and amino acids (including the excitotoxic amino acid glutamate) (5, 14). However, it is not clear whether these astrocyte volume regulatory mechanisms occur during neuronal damage *in vivo*.

Aquaporin Water Channels

Physiologists recognized long ago that water crosses the plasma membrane of many cell types (e.g., erythrocytes, kidney tubules) substantially faster than can be explained by simple diffusion. Over the past decade a family of related water-transporting proteins, called aquaporins (AQP), has been identified (15, 16). At least ten aquaporin water channels have been cloned from mammals and many more from amphibians, plants, yeast, bacteria and other lower organisms. The aquaporins are small (~30 kDa) hydrophobic proteins that assemble in membranes as tetramers. Each monomer, consisting of six membrane-spanning tilted α-helical domains with cytoplasmically oriented amino and carboxy-termini, contains a distinct water pore (17, 18). The aquaporins can be classified functionally into two groups. AQP1, AQP2, AQP4, AQP5 and AQP8 are mainly permeable to water. AQP3, AQP6, AQP7 and AQP9 are also water permeable, but in addition have significant permeability to small solutes such as glycerol (AQP3, AQP7 [aquaglyceroporins]) and larger neutral solutes (AQP9), and possibly under some conditions, to ions (AQP6).

The sites of aquaporin expression suggest a role in renal water reabsorption, CSF dynamics, aqueous fluid dynamics, glandular secretion, and other physiological processes. Humans with mutations in AQP2, the vasopressin-regulated water channel in the kidney collecting ducts, have the rare disease, hereditary nephrogenic diabetes insipidus, which manifests as severe polyuria (19). Unfortunately, aquaporin inhibitors suitable for use *in vivo* do not exist, which has made it difficult to define the role of aquaporins in organ physiology. However, recent phenotype studies in transgenic mice lacking AQPs 1–5 have been very informative (20, 21). For example, mice lacking AQP1, AQP2 or AQP3 have defective urinary concentrating ability (22–27), mice lacking AQP4 have impaired hearing (28), and mice lacking AQP5 have impaired secretion by salivary gland (29) and airway submucosal glands (30). The phenotype studies suggest that aquaporins are important for rapid, near-isosmolar fluid transport, as occurs in kidney proximal tubule and salivary gland, and for water transport when it is driven by established osmotic gradients, as in kidney collecting ducts. The phenotype studies have also shown that the tissue-specific expression of an aquaporin does not indicate physiological significance — for example, deletion of AQP4 in skeletal muscle and gastric parietal cells does not impair skeletal muscle function (31) or gastric acid production (32). The aquaporin null mice provide a useful tool for defining the role of aquaporins in fluid balance in the central nervous system.

Aquaporin Expression in the Brain

AQP1 and AQP4 are expressed strongly in the brain. In normal rat brain, AQP1 transcript and protein expression is restricted to the ventricular-facing surface of choroid plexus (Fig. 3A) (33, 34). AQP1 was initially cloned from

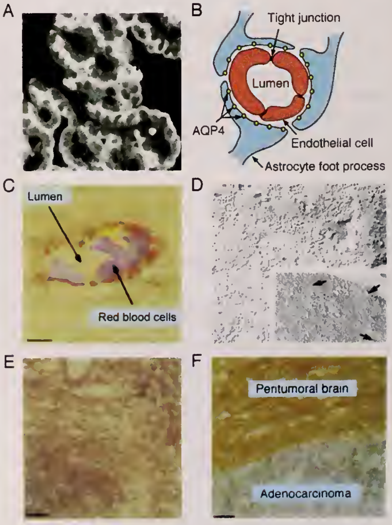

Fig 3. A. Immunofluorescence showing AQP1 protein expression in the apical surface of choroid plexus cells in rat. B. Diagram of a brain microvessel in cross section. Endothelial cells (red) are joined by tight junctions (black) and surrounded by astrocyte foot processes (blue). AQP4 water channels (circles) are expressed at the astrocyte foot processes. C. In normal human brain parenchyma AQP4 immunoreactivity (brown) is seen mainly around the microvessels. Bar: 10 mm. D. Freeze-fracture electron micrograph (E-face) of rat brain showing AQP4 square arrays in an astrocyte foot process. Inset shows arrays in P-face micrograph (arrows). E. Human glioblastoma multiforme immunostained for AQP4. AQP4 expression (brown) is not restricted to the perimicrovessel region, but is massively upregulated throughout the specimen. Bar: 10 µm. F. Metastatic adenocarcinoma in human brain showing marked AQP4 immunoreactivity (brown) in peritumoral brain. Bar: 10 µm.

human erythrocytes (35) and shown by several laboratories in heterologous expression and reconstitution studies to function as a water-selective transporter. It has been proposed that transport of ions (36) and carbon dioxide (37) through AQP1 occurs under some conditions, though such transport, if it occurs, is probably not of physiological significance (38). AQP1 protein has been visualized directly by freeze-fracture electron microscopy, as small intramembrane particles with a tetrameric structure (39). The expression of AQP1 in choroid plexus, taken together with the paradigms established from the mouse phenotype studies of non-neural tissues mentioned above, suggests that AQP1 plays a role in CSF secretion.

AQP4 is expressed in astrocyte foot processes near blood vessels in rat (40, 41) and human (42) brain (Figs. 3B, 3C), as well as in ependymal and pial surfaces in contact with CSF (41, 43, 44). This localization suggests that AQP4 plays a critical role in brain water balance. AQP4 was initially cloned from rat lung (45), and subsequently isoforms from rat brain (46) and orthologues from human (47) and mouse (48) were sequenced. AQP4 appears to be selective for the passage of water, and is unique among the aquaporins in its exceptionally high intrinsic water permeability (49) and its assembly in membranes in regular square arrays called orthogonal arrays of particles (OAPs) (Fig. 3D). The involvement of AQP4 in OAP formation was originally proposed because of the expression of AQP4 in tissues known to contain OAPs (44), and it was later proven in heterologously expressing cell cultures (50) and as a result of the absence of OAPs in AQP4 null mice (51). Immunogold-label freeze-fracture electron microscopy confirmed the presence of AQP4 in OAPs in the brain (40, 41).

Other aquaporins may also be expressed in the brain, though the evidence is less compelling. In rats (52) and mice (53), AQP9 protein has been detected in cells lining the cerebral ventricles, including ependymal cells and tanycytes, and possibly at low levels in astrocytes. There may be other as yet unidentified aquaporins in the brain, and some non-aquaporin proteins, such as glucose, urea and ion transporters, may transport small amounts of water.

Indirect Evidence for a Role of Aquaporins in Brain Edema

A number of studies indicate that the expression of aquaporins in the brain is sensitive to brain injury, swelling and other experimental maneuvers. In rodents, AQP4 expression in astrocytes is upregulated in response to cerebral edema caused by brain injury (54, 55), focal brain ischemia (56) and hyponatremia (57). AQP4 expression is also upregulated in edematous human tumors (Figs. 3E, 3F), where AQP4 loses its polarity and redistributes throughout the astrocytes. After middle cerebral artery occlusion in rats, the increase in AQP4 transcript expression parallels brain edema, as monitored by magnetic resonance imaging (56). In rat models of brain injury (54), increased AQP4 expression occurs in astrocytes at sites where the blood-brain barrier is disrupted. Increased AQP4 expression thus appears to occur in edematous brain regardless of the underlying cause of edema. If AQP4 contributes to brain edema, then its upregulation may be a maladaptive response, as is the case for upregulation of AQP2 in the kidney, in some fluid-retaining states.

Expression of AQP1 protein has been reported in endothelial cells in rat models of glioblastoma and metastatic brain cancer (58). A microarray study of differential gene expression has also found increased AQP1 transcript expression in glioblastoma, which has been confirmed by AQP1 immunohistochemistry on tumor samples (59). AQP1 expression in microvessels of neoplastic brain may contribute to increased blood-brain barrier water permeability in aggressive brain tumors. In normal brain, AQP1 expression in choroid plexus is downregulated in mice exposed to hypogravity during spaceflight (34), which may be a compensatory response to changes in CSF distribution. It is not known whether AQP1 expression in choroid plexus is altered in response to elevated ICP.

After transient focal brain ischemia in mice, AQP9 protein, which is normally only weakly expressed in mouse astrocytes, appears to be upregulated in astrocytes in peri-infarct areas (53). Since AQP9 is permeable to water and lactate, it was proposed that AQP9 may be involved in reperfusion edema associated with lactic acidosis. However, due to the lack of aquaporin channel blockers it is unclear whether the increased expression of AQP4, AQP1 and AQP9 in edematous brain is functionally important or represents an epiphenomenon.

Regulation of Aquaporin Expression

Little is known about the molecular mechanisms involved in regulated aquaporin expression in brain. Developmental studies indicate that AQP4 protein expression in rat brain is very low before birth and increases steadily over the first two weeks *post partum* (60). AQP4 expression in astrocytes appears to be cell cycle-dependent and only expressed in the G0/G1 phase (61). The human AQP4 gene, located on chromosome 18, encodes proteins of 31 and 34 kDa that are produced by alternative splicing and separate promoters (62). Both isoforms are expressed in the brain, but the smaller isoform is the one mainly found in other tissues. The significance of the different AQP4 isoforms is unclear.

Normal brain astrocytes, which are in contact with endothelial cells and neurons, selectively express AQP4 in astrocyte foot processes adjacent to endothelial cells. It is thus possible that the polarized AQP4 expression in astrocytes may be regulated by factors released by neurons and/or endothelial cells. This hypothesis is supported by the observation that AQP4 expression is not polarized in reactive (42) and cultured (63) astrocytes, which have no contact with endothelial cells or neurons. Protein kinase C has been shown to mildly reduce AQP4 water-transporting activity (64) and transcript expression (65). However, no molecular-level information is available about other potential regulators of AQP4 expression.

AQP1 is expressed in endothelial cells of aggressive brain tumors, but not in normal brain endothelium (58, 59). AQP1 expression in endothelial cells might be induced by vasogenic substances, such as vascular endothelial growth factor and scatter factor/hepatocyte growth factor, which are released by tumor cells. The AQP1 promoter, sequenced from erythroleukemia cells (66), contains glucocorticoid response elements, raising the possibility that the antiedema action of corticosteroids in brain tumors may be mediated partly by changes in AQP1 expression in tumor vasculature.

Direct Evidence for a Role of AQP4 in Brain Edema

Recently, the hypothesis was tested that AQP4 plays a role in the accumulation of brain water in response to two established neurological insults: acute water intoxication (producing hyponatremia) and ischemic stroke (producing brain edema by a combination of vasogenic and cytotoxic factors) (67). Experiments were done on AQP4 null mice, which are grossly phenotypically normal and do not manifest neurological abnormalities, altered blood-brain barrier properties, or impaired osmoregulation (67, 68). Brains from AQP4 null mice show reduced osmotic water permeability, as measured in isolated membrane vesicles (68) and brain slices (69). AQP4 deletion in mice conferred remarkable protection from brain edema. The survival of AQP4 null mice after water intoxication was greatly improved (Fig. 4A), which corresponded to significantly reduced brain swelling, particularly in astrocytic foot processes. In addition, at 24 hours after brain ischemia produced by permanent middle cerebral artery occlusion, there was improved clinical outcome and much less brain swelling (Fig. 4B).

These experiments provided the first direct evidence that AQP4 is important in the formation of brain edema. It has been proposed that AQP4 is a potential target for drug discovery (70). AQP4 inhibitors might slow the accumulation of

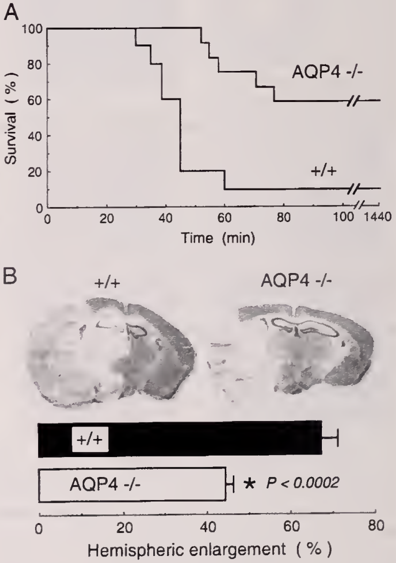

Fig 4. Reduced brain edema in AQP4 null mice after acute water intoxication and ischemic stroke. A. Survival of wild-type vs. AQP4 knockout mice after acute water intoxication produced by intraperitoneal water injection. B. (top) Brain sections of mice at 24 hours after ischemic stroke produced by permanent middle cerebral artery occlusion. Note midline shift and marked edema in brain from wild-type mice. (bottom) Average hemispheric enlargement expressed as a percentage determined by image analysis of brain sections. (Adapted, with permission, from ref. 67).

brain water, thereby reducing the morbidity and mortality of patients with neurological disorders.

Future Directions

Additional direct evidence supporting the involvement of aquaporins in brain edema is needed; in the immediate future, such evidence is likely to come from studies using aquaporin null mice. The postulated role of AQP1 in CSF production requires direct experimental verification. Although an important role for AQP4 in brain edema caused by water intoxication and focal brain ischemia has been demonstrated (67), the role of AQP4 in brain edema resulting from head injury, brain tumor and peripheral organ failure has not yet been explored. Kinetic measurements are needed to determine whether AQP4 deletion exacerbates brain edema early following head injury, and perhaps impairs the reabsorption of brain water later. Aquaporin inhibitors, which are likely to be identified by high-throughput screening or other approaches, may thus be indicated in the early phases of brain swelling. Finally, further work is needed to obtain molecular-level information about mechanisms involved in the regulation of brain aquaporin expression in tumor and other edema-inducing conditions.

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Editor's Note

THE INCREASING PROBLEM of hip fractures in the elderly is a strong inducement to start emphasizing hip fracture prevention. Two major pathways for hip fracture prevention are preventive measures and early treatment for osteopenia, and mechanical attenuation and dissipation of force energy from a fall.

The literature dealing with osteopenia is extensive, but information on prevention of hip fractures with hip protectors is scant (1, 2). Of note is a recent article in the *New England Journal of Medicine* by Kannus P. et al. (3) which corroborates earlier studies on the effectiveness of hip protectors in preventing hip fracture from a fall. Although one might take issue with the contention that most hip fractures result from a sideways fall directly onto the trochanter, the statistics in three different studies are compelling. Hip protectors do give considerable protection against hip fractures.

Two major problems have been noted in trying to use hip protectors for hip fracture prevention. The first is that there is poor compliance in using the device, with one study showing that only 24% of the treatment group wear the protector regularly. The other problem is that, at this time, the hip protectors are not commercially available in the United States. This is extremely hard to understand, since in these days of cost containment, the prevention of only one hip fracture would more than pay for one hundred hip protectors.

It has been estimated that the use of hip protectors by eight at-risk patients would prevent one hip fracture. We would be well advised to place more emphasis on prevention and try to devise and manufacture simple, inexpensive, effective and user-friendly hip protectors.

Sherman Kupfer, M.D.
Editor-in-Chief

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Treatment of Hip Fractures in the Elderly — The Decision Process

Sheldon Lichtblau, M.D.

Abstract

A fractured hip in an elderly person is usually treated by performing one of various surgical procedures. There are also choices in postoperative routines involving weight-bearing status, blood transfusions, anticoagulation measures and pain control. Several factors influence the selection of treatment and postoperative routine. Among them are the preoperative health status and mobility of the patient, the type of fracture and the quality of the bone. The relationship between these factors and the various treatments is explored in an effort to show how and why an orthopedist decides on a particular treatment routine. Understanding these relationships should enable the nonorthopedic members of the hip fracture team to participate more effectively in the care of the patient.

Key Words: Femoral neck fractures, hip fractures, treatment options.

The care of a patient with a fractured hip has generally been considered the responsibility of an orthopedist. Recently, however, it has evolved into a team effort. Initially, the team consists of the primary care physician and the orthopedist. If surgery is the elected treatment, the anesthesiologist becomes an integral member. After surgery, the team expands to include physical therapists, nursing staff, nutritionists, and geriatric psychiatrists, all of whom have important roles in restoring the patient to prefracture status. Their contributions may be enhanced by a better understanding of the different treatment options available to the orthopedist. Such options may range from the simple procedure of inserting screws into the femur across the fracture, to a partial or even total hip replacement.

Postoperative routines may also vary, depending on the fracture type and surgical procedure employed. Some patients are allowed to bear full weight on the injured limb, while others may be kept off the leg for prolonged periods of time. Some fractures require frequent blood transfusions. Anticoagulation measures range from aggressive chemical measures with close monitoring, to the use of compression stockings and aspirin. The variety of fractures and treatments result in a spectrum of requirements for pain medication after surgery, as well as for nutritional supplements and even psychiatric medications.

The following material provides a brief overview of the decision-making process employed by the orthopedist when selecting one surgical treatment over the others. Common problems and complications of each procedure are discussed. This information should offer the nonorthopedic members of the team a better understanding of the intended intervention. In addition, it covers preoperative factors that the primary care physician and anesthesiologist use to evaluate the patient's readiness for surgery, factors that are also important in helping the orthopedist achieve a successful outcome.

The decision to operate on a fractured hip is usually the result of a collaboration between the orthopedist and the primary care physician. In the days before surgical intervention, a fractured hip in an older person was almost always fatal. This tragic situation was improved with the introduction of spica cast treatment and traction in the early twentieth century, but the mortality rate still remains greater than 50% with nonoperative treatment (1, 2). Current thinking is that an early surgical procedure offers the best chance for the patient's survival and well-being (3–5). Surgery for a fractured hip is usually considered to be an emergency procedure and is therefore performed as soon as the patient can be medically stabilized. However, since one study (6) has shown that the one-year mortality rate is higher for those pa-

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tients operated on within the first 24 hours, the surgery is generally performed between 24 and 48 hours after the injury. To my knowledge, there is no study challenging this finding.

Preoperative Factors

There are four important preoperative factors that influence the treatment of an elderly patient with a fractured hip: the general health of the patient, the type of hip fracture sustained, the prefracture mobility of the patient, and the quality of the patient's bone.

General Health

The current health of the patient is the most important factor in deciding when to operate and what operation should be performed.

Once the decision to perform surgery is made, the anesthesiologist joins the primary care physician in evaluating the patient's preoperative status. Their collaboration determines not only the choice of anesthesia, but also whether to perform the surgery now or later. Medical conditions such as acute myocardial infarction, acute cerebrovascular accident, severe electrolyte imbalance, high levels of anticoagulation and severe anemia add significant risk to the surgical procedure. In these situations, the surgery is delayed until the condition is stabilized and the risk reduced. In our experience, the mild degree of anemia and minor electrolyte disturbances frequently found in the elderly do not seem to diminish the likelihood of a favorable outcome. We have found that preoperative transfusion is necessary when hemoglobin is 8 g/dL or less, but surgery need not be delayed if the hemoglobin is at least 9 g/dL — when transfusion can be given intraoperatively. If the hemoglobin is more than 10 g/dL, a decision to transfuse can be made postoperatively. The comorbidity of vascular disease (coronary artery, cerebral vascular) may require modification of these criteria. A randomized study of blood transfusions seems to validate this approach (7).

Types of Fracture

Hip fractures are intracapsular, intertrochanteric or subtrochanteric, depending upon the location of the fracture on the femur (Fig. 1). These designations are further subdivided according to whether the fractures are displaced or non-displaced. In the group of intertrochanteric fractures, a further classification is made according to the amount of comminution (fragmentation of the fracture). This typing and subtyping helps determine the optimal surgical procedure and also helps predict the potential for complications.

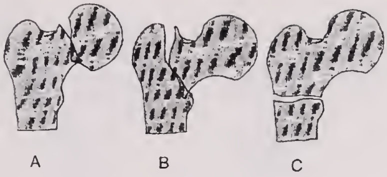

Fig. 1. Type of hip fractures.
A. Femoral neck; **B.** Intertrochanteric; **C.** Subtrochanteric.

Prefracture Mobility

Patients are generally considered community ambulators (with or without external support), household ambulators or non-ambulatory. If patients were fully ambulatory or household ambulators, the goal of the surgery is to restore them to the degree of ambulation which existed prior to hip fracture. If patients were non-ambulatory, surgery is performed to provide relief of pain and allow mobilization. Thus, it would be inappropriate to do a hip replacement for a hip fracture on a non-ambulatory patient, when simple removal of the femoral head may provide the desired pain relief.

Bone Quality

Elderly patients with hip fractures have varying degrees of osteopenia (osteoporosis or osteomalacia), which is usually apparent on x-ray of the hip. The severity of bone weakness is to a large degree related not only to nutrition and hormonal factors, but also to how active the patient had been prior to the fracture. For patients who were fully ambulatory and for most household ambulators, the bone strength is usually adequate for any surgical procedure. Non-ambulatory patients, however, often have severe osteopenia, so that their bones are too soft for usual internal fixation. Special materials or techniques, such as methylmethacrylate to enhance the fixation, or modified internal fixation may be utilized (8).

Fracture Healing

Bone healing occurs by the gradual transformation of the blood clot between the fragments into an organized cartilaginous callus, onto which calcium is deposited and gradually remodeled into bone. The requirements for this process include good apposition of the bony surfaces and maintenance of this apposition until the union is solid. With respect to femoral neck fractures, contact is mainly between compact cortical bone surfaces (Fig. 2 — site 1) which do not unite readily. On the other hand, trabecular bone, which presents a much larger surface area than cortical bone (Fig. 2 — site 2), bridges more quickly. This is the reason intertrochanteric fractures, which present large areas of trabecular bone at the fracture site, are more apt to heal than femoral neck fractures, where the contact is mainly between cortical bone surfaces. The healing of a fractured hip has been described as a race between the stress forces at the fracture and the body's ability to heal the fracture.

Although the ultimate goal of hip fracture treatment is for the patient to return to prefracture mobility with either a healed fracture or a prosthetic device, the immediate goal of treatment is mobilization of the patient to prevent pneumonia, decubiti, phlebitis and pulmonary embolism. Therefore, the treatment selected must permit early postoperative mobilization of the patient. Much of contemporary orthopedic (9, 10) on hip fracture treatment deals with the relative merits of orthopedic devices in holding fracture reduction while permitting movement and weight bearing on the hip.

An important but often neglected element in the healing process is the patient's nutritional status. Studies have shown that many patients with fractured hips are malnourished on admission to the hospital (11, 12). Nutritional supplements are not a routine part of the postoperative regimen, so supervision by a nutritionist is often desirable. In addition to addressing special dietary needs, the nutritionist arranges for protein and vitamin supplements, and in cooperation with the nursing staff, monitors the patient's actual intake. Choosing foods that a patient likes can make the difference between an adequate and an inadequate diet.

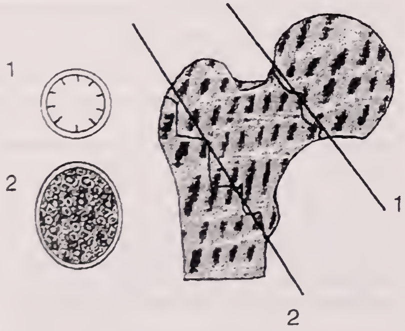

Fig. 2. Cross-section of a fractured hip at the femoral neck (site 1) showing a circle of cortical bone, and at the intertrochanteric area (site 2) showing an oval filled with trabecular or cancellous bone.

Osteoarthritis and Osteoporosis in Hip Fractures

The presence of osteoarthritis in a hip seems to influence the type of fracture sustained. My clinical experience in the treatment of almost two thousand hip fractures has shown that hips with osteoarthritis tend to sustain an intertrochanteric or subtrochanteric fracture after a fall. This has been indirectly corroborated by a study of femoral neck fractures which showed that they did not occur in arthritic joints (13).

In some fractured hips with pre-existing arthritis, a hip replacement can be considered instead of internal fixation, especially if the hip was painful before the fracture.

Osteoporosis plays an important part in the causation of hip fractures. In a study of bone mineral density (BMD) in patients with hip fractures, the mean BMD was more than two standard deviations below age- and sex-matched controls, with the primary target for bone loss being the femoral neck (14). However, with current increased awareness of osteoporosis and medical prophylaxis and treatment, orthopedists are seeing fewer cases of spontaneous fracture, e.g., "I was just standing/walking and suddenly my leg collapsed and I fell."

It has been shown that after treatment of a hip fracture, the non-fractured hip becomes even more osteoporotic for at least a year, possibly as a result of decreased mobilization postoperatively. This has contributed to the high incidence of second hip fractures seen the first year after a hip fracture (15, 16).

If the patient can avoid a second hip fracture, there is a good chance that after the first year, remineralization will start and the BMD may return to prefracture levels. A postoperative longitudinal study of 55 patients who had BMD studies one year after hip fracture was able to show the great loss of mineralization known to occur in the first year. Twenty-one of these patients returned for BMD studies five and six years later. Of the 16 who had not had a second hip fracture, 60% were seen to have a bone density at or above baseline. Larger studies are needed to elucidate the important factors in this remineralization process (17).

Treatment for osteoporosis after a hip fracture starts with nutrition. Adequate protein, vitamin and mineral intake is required, and supplements should be prescribed when the diet seems insufficient. Bone-enhancing drugs such as alendronate or calcitonin may be added to the regimen if tolerated. Recently, low doses of parathyroid hormone have been shown to be helpful (18). A low-impact exercise routine, which is known to aid remineralization, should be recommended for the physically capable elderly.

Treatment of Hip Fractures

As mentioned earlier, prior to the introduction of surgical treatment for hip fractures, the mortality rate in the elderly with this condition was extremely high. Today surgery is the usual treatment for a fractured hip. Nonoperative treatment, consisting of traction, mobilization from bed to chair, or positioning in bed, is reserved for very-poor-risk patients who might not survive surgery. Most often these are patients with advanced Alzheimer's disease who are already non-ambulatory. Since they are already virtually bedridden, they seem to be at less risk than ambulatory patients for the complications of enforced bed rest, e.g., pneumonia, phlebitis and pulmonary embolism. They may live long enough for their fractures to heal, but not surprisingly, their one-year survival rate is poor.

The type of operation for a fractured hip depends on the location and degree of the fracture. As mentioned earlier, hip fractures are either intracapsular, intertrochanteric or subtrochanteric. Understanding the differences allows a better appreciation of the problems inherent in each type.

Intracapsular Fractures

Treatment of an intracapsular fracture of the femoral neck depends on the degree of displacement of the fracture. The Garden classification (Fig. 3) has proven to be useful in determining the treatment for a femoral neck fracture, since it not only indicates the amount of contact between the fragments and the inherent stability of the fracture, but also seems to correlate with damage to the blood supply to the femoral head (19). Thus, the impacted (Garden I) and undisplaced (Garden II) fractures have excellent bony contact, inherent stability, and no disruption to the blood supply to the femoral head. Such fractures need only be stabilized against the rotation forces which occur with flexion and extension of the hip, to prevent them from displacing. Fixation is accomplished by inserting three screws across the fracture (Fig. 4).

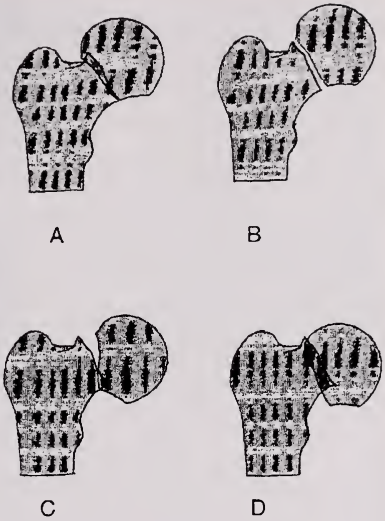

Fig. 3. Femoral neck (intracapsular) fractures (Garden Classification).
A. Impacted — Garden I; **B**. Complete — Garden II; **C**. Mildly displaced — Garden III; **D**. Completely displaced — Garden IV.

These fractures rarely require blood transfusion postoperatively, because there is very little blood loss at the fracture or from the surgery itself. Postoperative mobilization is usually rapid, because the hip fixation decreases the pain.

The moderately displaced fracture (Garden III) is reducible because contact between the fragments is partially maintained, but because the capsule is torn, the blood supply to the femoral head may be compromised to some degree. This may lead to aseptic necrosis of the

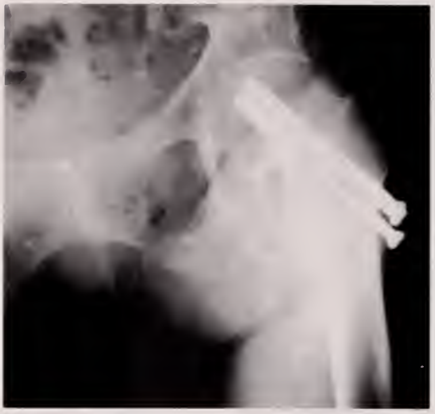

Fig. 4. Cannulated screws used to fix Garden I and Garden II fractures of the femoral neck.

femoral head or non-union at the fracture. Also, even after reduction and fixation, this fracture may be unstable and go on to displace. For these reasons, hemiarthroplasty (prosthetic replacement of the femoral head) is often selected as the treatment of choice in the elderly. This avoids the problems of non-union and aseptic necrosis, while permitting immediate mobilization and weight bearing (Fig. 5).

The completely displaced fracture (Garden IV) has great difficulty healing after reduction and fixation, because reduction at best brings two circles of cortical bone into contact (Fig. 2). Most often, perfect reduction cannot be achieved. In addition, the blood supply to the femoral head is severely compromised, leading to aseptic necrosis and collapse of the femoral head after union has occurred (Fig. 6). For these reasons, most orthopedists treating this fracture in patients older than sixty-five, choose to do a hemiarthroplasty.

Even in younger patients, for whom there is a strong reluctance to do a hemiarthroplasty, there is a high failure rate for reduction and fixation from either non-union of the fracture or avascular necrosis of the femoral head.

In Garden III and IV fractures, the capsule is torn and does not tamponade the bleeding from the fracture, as does the intact capsule in Garden I and II fractures. Therefore, many of these patients are admitted with swollen thighs and anemia. In addition, the surgery for hemiarthroplasty may entail a fair amount of blood loss. Thus, these patients often require blood transfusion postoperatively and are more vulnerable to electrolyte imbalances.

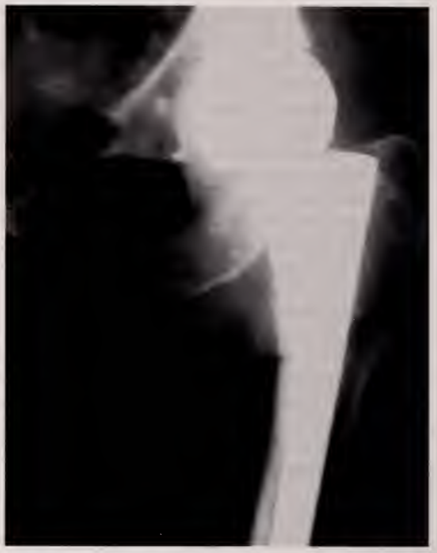

Fig. 5. Hemiarthroplasty — used for Garden III and Garden IV femoral neck fractures.

The surgery for hemiarthroplasty necessitates putting the involved limb in a position in which the veins may be kinked or compressed, resulting in a high incidence of phlebitis and/or pulmonary embolism. However, anticoagulation itself has major risks (internal bleeds, wound hematoma, neuropraxia, etc.). There is as yet no therapeutic regimen that is universally accepted. Low-molecular-weight heparin is becoming more popular because monitoring of the coagulation status may not be necessary.

Intertrochanteric Fractures

An intertrochanteric fracture is a break in the femur lateral to the base of the neck, an area filled with cancellous bone (Fig. 2). When the surfaces are apposed, healing of the fracture is promoted if the apposition is well maintained. The device most commonly used to maintain apposition is a form of screw or blade, and side plate. Most orthopedists use a form of the compression screw (Fig. 7). However, the Gamma nail, an intramedullary device that increases the

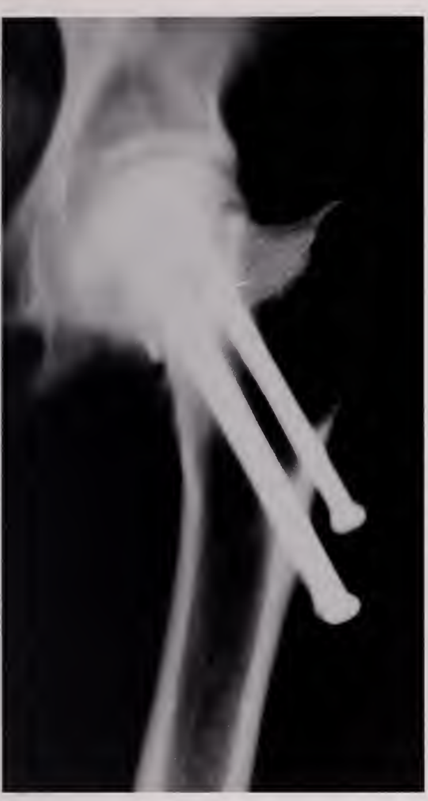

Fig. 6. Reduced and pinned displaced femoral neck fracture: early non-union and avascular necrosis.

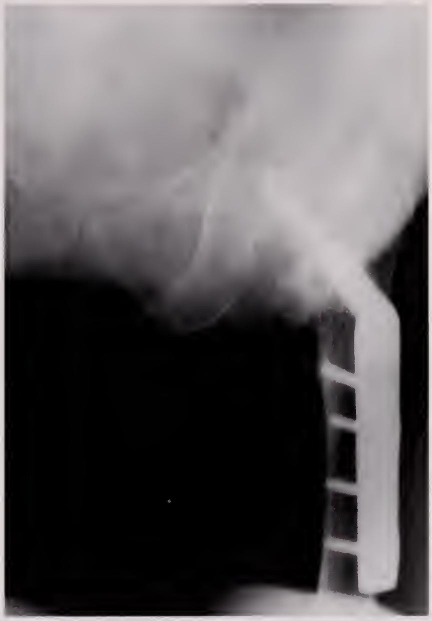

Fig. 7. Compression screw device used to fix an intertrochanteric fracture.

stability of an unstable fracture, may soon become the fixation of choice (20–22). This fixation had a high complication rate when first introduced, but modifications seem to have markedly decreased these complications, which consisted of fractures during or shortly after insertion.

Intertrochanteric fractures are classified according to the degree of comminution (Fig. 8). This determines the inherent stability of the fracture and may play an important role in the postoperative management. For example, the two-part fracture and the three-part fracture with a small, lesser trochanter fragment are relatively stable fractures. A compression screw fixation will usually secure the fracture and allow full weight on the limb while the fracture heals. These fractures have varying amounts of blood loss, depending on the degree of displacement at the fracture. The amount of swelling in the thigh at the time of admission is often the best indicator as to the potential need for pre- or post-operative blood transfusion.

Three-part fractures with large third fragments and four-part fractures are inherently unstable fractures, capable of displacing after reduction and fixation. These fractures are more frequent in osteoporotic bone and have a higher incidence of orthopedic complications such as screw penetration of the femoral head or cutting out of the femoral head. For this reason, many orthopedists protect the fixation by insisting on a period of healing before allowing full weight on the injured leg.

In this group of fractures, considerable bleeding may occur and result in local venous compression. The loss of blood during the surgical procedures may be problematic and require transfusions. Postoperative chemical an-

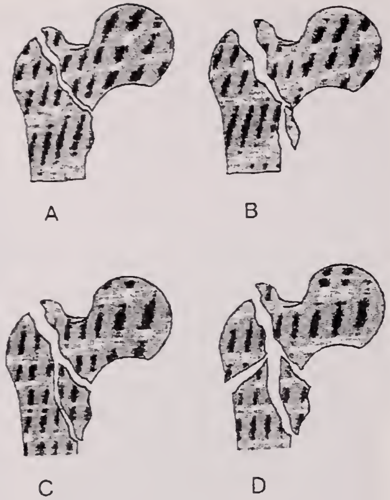

Fig. 8. Intertrochanteric fractures.
A. Two-part; **B**. Three-part, small third fragment; **C**. Three-part, large third fragment; **D**. Four-part.

ticoagulation is routine, to reduce the risk of pulmonary embolism from phlebothrombosis.

Subtrochanteric Fractures

Subtrochanteric fractures are actually fractures of the upper end of the femoral shaft (Fig. 9). They are often transverse. The main fixation devices are intramedullary nails (Fig. 10) and compression screws with long side plates (Fig. 11). The intramedullary nail is mechanically more stable, but when there is a trochanteric component to the fracture that destabilizes the proximal fixation, the screw and side plate become the treatment of choice. A more horizontal screw is often used to exert compression at the fracture.

These fractures and the surgery required to fix them may be accompanied by a great deal of bleeding. Multiple transfusions may be required. Anticoagulation is necessary.

The postoperative management for various fractures and surgical procedures has already been mentioned, but is worth some elaboration.

Postoperative Management

Following surgery for a fractured hip, the most important treatment is mobilizing the patient out of bed into the upright position. Whether this will be from bed-to-chair, or actual walking, depends on the postoperative weight-bearing status.

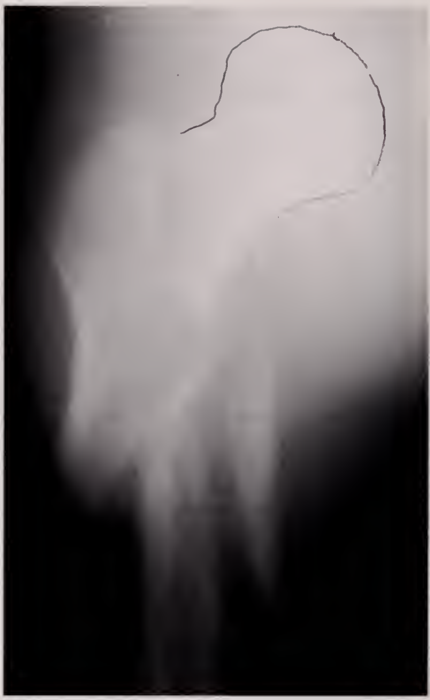

Fig. 9. Comminuted subtrochanteric fracture (femoral head has been highlighted).

Postoperative Weight-Bearing Status

Bearing weight on the operated fractured hip has multiple advantages. It not only contributes to fracture healing, but also helps maintain the muscular strength, general health, morale and agility of the patient. For the elderly, who are often at risk in these areas, these are important goals.

For stable fractures, which include the two-part intertrochanteric fractures, the three-part fractures with small third fragments, and the Garden I and Garden II femoral neck fractures, there is general agreement that immediate postoperative weight bearing should be attempted as tolerated. This also applies to patients who have had hemiarthroplasties. It is in the man-

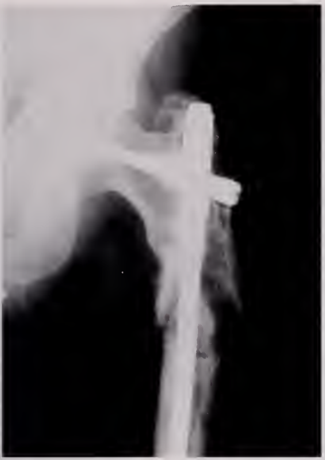

Fig. 10. Subtrochanteric fracture fixation with an intramedullary device.

agement of the unstable fractures that there is controversy. Unstable fractures, which are more prone to displacement after surgery, include three-part intertrochanteric fractures, four-part fractures, and Garden III fractures treated by internal fixation.

Some authorities consider non-weight-bearing to be the best option for minimizing forces of destabilization, thereby allowing the fracture to heal (23). On the other hand, proponents of early weight bearing claim that non-weight-bearing activities, such as getting out of bed or turning in bed, can be just as stressful at the fracture site as bearing weight on the limb, or even more so. Thus, their recommendation is for immediate weight bearing as tolerated following fixation (24). The biomechanical basis for the second group's recommendations has been extrapolated from *in vivo* studies of stresses on an internal fixation device (25). Since these measured stresses may not reflect the actual stresses at the fracture site, many other orthopedists, myself included, restrict weight bearing whenever there is concern regarding stability of the repair. New stress-strain studies on unstable intertrochanteric fractures are needed.

Implicit in "weight-bearing as tolerated" is the premise that perception of pain will prevent the patient from putting enough weight on the limb to challenge the fixation. The failures of fixation that occur show that this is not always true. The example of a well-fixed but unstable fracture that displaced when full weight was encouraged immediately is shown in Figs. 12 and 13. Fixed fractures can displace even without weight bearing, but the degree of displacement is usually not enough to preclude healing and a painless hip.

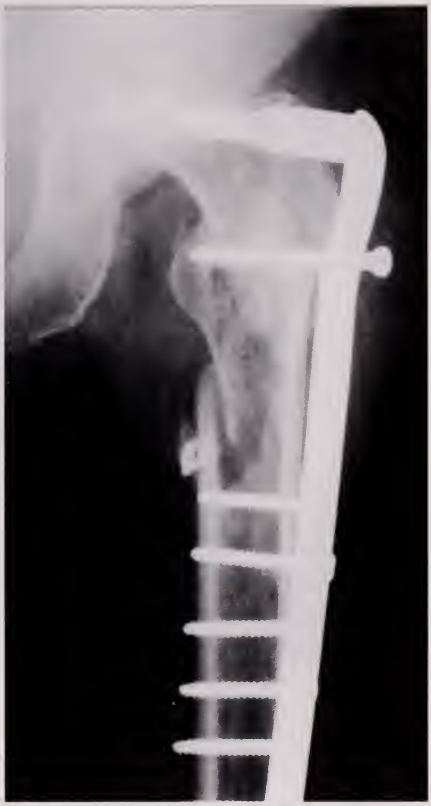

Fig. 11. Comminuted subtrochanteric fracture fixation with a horizontal compression screw and long side plate.

Pain Management

Postoperative pain management is a difficult problem for the physician, especially for those elderly patients who are very confused. Often, the medication either increases confusion and agitation or makes the patient very somnolent. On the other hand, undermedicating pain is inappropriate and should be avoided. The team should try to achieve adequate pain

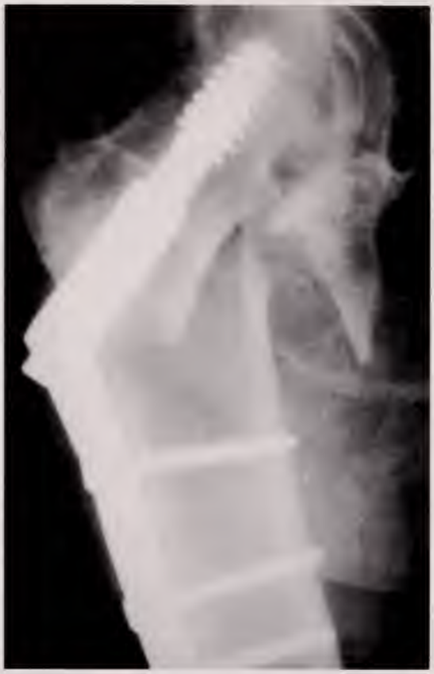

Fig. 12. A well-fixed but unstable intertrochanteric fracture.

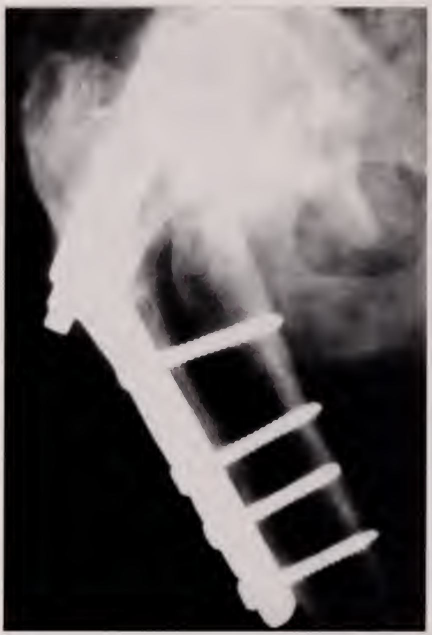

Fig. 13. Premature weight-bearing resulted in screw cutting out of the head.

control while minimizing the adverse effects of the medication. The anesthesiologist and geriatric psychiatrist can be helpful in selecting and titrating the appropriate medication. For the mentally intact patient, patient-controlled analgesia decreases the patient's helplessness and allows the patient to participate in the healing process.

Whether patients with dementia perceive pain as clearly as do those without dementia is uncertain; a recent publication suggests that they do (26). On the other hand, orthopedists find that senile patients with well-fixed, unstable hip fractures who are allowed full weight on the leg have a much greater chance of displacing the fracture and fixation than do the totally lucid patients. In my opinion, decreased perception of pain is the most likely reason.

Prevention of Infection

Use of antibiotics intraoperatively has become routine with most orthopedists. In uncomplicated fractures, one day of postoperative antibiotics seems to be adequate (27). Where there are co-morbidities, especially pulmonary or urinary, longer periods of treatment may be employed. Since urinary tract infections are often not eradicated by the antibiotics alone, combination with a urinary antiseptic may be required (28). Despite the fact that repeated catherizations have been shown to be safer than indwelling catheters (29), the Foley catheter is the usual post-hip-fracture routine, in most hospitals. This is probably because it is less labor intensive.

Electrolytes

Imbalance of the serum electrolytes is related to the patient's mental and nutritional status. The confusion and agitation or somnolence often seen in senile people can mask an electrolyte problem. Initially, daily postoperative laboratory tests may be required to identify and treat the problem early and expeditiously.

Prevention of Hip Fractures

Prevention of hip fractures has become a very important health issue. It has been shown that using commercially available hip protectors in those at risk dramatically decreases the incidence of hip fractures following falls (30, 31). The major problems with hip protectors, at present, are lack of patient compliance and cost (32). Reasons for noncompliance are discomfort, appearance and interference with daily activities (e.g., toilet). Also, dealing with the complexities of putting on and taking off protectors discourages some elderly patients. Current efforts should be directed at testing and developing low-cost, low-profile, effective protection that is no more difficult to get into or remove than underwear. In the current age of "bubble wrap," this should not be an insurmountable task.

Conclusion

The current survival rate in the elderly population for one year, following a hip fracture, is about 75%. It decreases to 45% at six months in the population with advanced Alzheimer's disease (33). Whether improved treatment of osteoporosis, maintaining better nutrition and encouraging physical exercise and mental stimulation in aged patients can lead to more favorable outcomes is yet to be determined.

Summary

Recovery following a hip fracture is dependent upon the treatment of the fracture. An appropriate operative procedure is most often an important part of the treatment. Therefore, the non-orthopedists on the health care team need to understand the factors taken into consideration in the choice of the surgical procedure and the postoperative management for an elderly patient with a fractured hip.

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Catamenial Hemoptysis and Pulmonary Endometriosis:

A Case Report

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and Fred Rosner, M.D.[7,8]

Abstract

Hemoptysis can be caused by a variety of pulmonary diseases, including parasitic infections, tuberculosis, chronic bronchitis and malignancies. Rarely, pulmonary endometriosis can present with hemoptysis and pose a diagnostic problem to clinicians. Pulmonary endometriosis can easily be confused with other clinical entities, including pulmonary embolism, pneumonia and pneumothorax. Histopathologic confirmation is difficult, since the bleeding site is not easy to locate. However, a presumptive diagnosis of pulmonary endometriosis can be made with a typical clinical history. Even so, medical therapy may be problematic, with recurrence of symptoms despite hormonal ablation. We report a case of presumptive pulmonary endometriosis in a 32-year-old woman with a history of an induced abortion, who presented with catamenial hemoptysis (approximately one tablespoon per episode) occurring in the first 3 days of menstruation over an 11-month period. She was treated with an oral contraceptive for two months. No recurrence of hemoptysis was noted during 18 months of follow-up. The approach to diagnosis and treatment of pulmonary endometriosis is reviewed.

Key Words: Pulmonary endometriosis, catamenial hemoptysis, oral contraceptives, computerized tomography.

Introduction

ENDOMETRIOSIS IS DEFINED as the presence of endometrial glands and stroma outside the uterine cavity. Because the growth and maintenance of these implants depend on ovarian steroids, this condition occurs exclusively in women during their reproductive years or in women receiving estrogen replacement therapy (1).

Pelvic structures, including the ovaries, cul-de-sac, broad ligaments and uterosacral ligaments, are usually involved. However, endometrial tissue can occasionally be found outside the pelvis, in the thorax, brain, abdomen and skin. Because of the preponderance of involvement of pelvic organs, the presenting symptoms usually include pelvic pain, dysmenorrhea and menstrual abnormalities. While pelvic endometriosis may affect up to one percent of women, thoracic endometriosis is a rare disorder. We report a case of pulmonary endometriosis presenting with catamenial hemoptysis (coughing of blood coincident with the time of menstruation) which was clinically attributed to this condition. Although hemoptysis resolved after treatment of the patient with oral contraceptives, this therapy is not always curative.

Case Report

A 32-year-old woman (gravida 3, para 2) with a history of an induced abortion 3 years before, presented with catamenial hemoptysis. She described episodes of hemoptysis (approximately one tablespoon per episode) occurring in the first 3 days of menstruation regularly for 11 months. Between menstrual cycles the patient was asymptomatic. Regular menses of five days' duration occurred every thirty days. She was a nonsmoker and denied any history of lung disease. In particular, she denied fever, purulent sputum production, night sweats or exposure to individuals with known infectious pulmonary diseases. She had not traveled outside of the local area.

Results of the physical examination were normal. The patient had mild anemia (hemoglobin 11.5 g/dL). The chest x-ray was normal, but computerized tomography (CT) of the chest revealed a 1.5 cm, ill-defined infiltrate in the left upper lobe posterior segment (Figure). A bronchoscopic airway inspection did not reveal a source of bleeding. Tuberculosis skin testing and sputum acid bacilli cultures were negative. A pelvic ultra-

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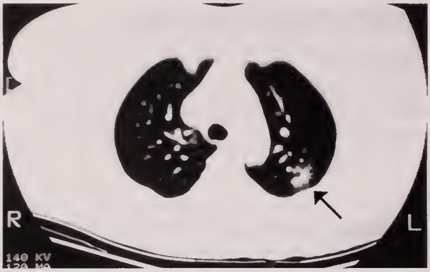

Figure. CT scan of the chest during menstruation. An ill-defined infiltrate (arrow) is seen in the posterior segment of the left upper lobe.

sound revealed no evidence of endometriosis. A presumptive diagnosis of pulmonary endometriosis was made, based on the clinical features (see below). The patient's menses stopped temporarily during a two-month treatment with an oral contraceptive, ethinyl estradiol/norethindrone acetate (Loestrin®, Parke Davis, Morris Plains, NJ). Hemoptysis did not recur during 18 months of follow-up.

Discussion

The present case demonstrates clinical features suggestive of pulmonary endometriosis. Because the specific sites of pulmonary endometriosis are difficult to localize for biopsy, a histopathologic diagnosis was not made in this case. Rather, a presumptive diagnosis of pulmonary endometriosis was based on classic clinical features. Given the characteristic presentation of this disease, the diagnosis remains presumptive. Thoracic endometriosis is a rare disorder. Since its initial description in 1956 (2), approximately 110 cases have been reported. The four presentations of thoracic endometriosis are catamenial pneumothorax, catamenial hemothorax, catamenial hemoptysis and pulmonary nodules. Catamenial pneumothorax, the most common form of thoracic endometriosis, occurs in 73% of patients (3). Catamenial hemothorax is less common (14%), followed by catamenial hemoptysis (7%) and lung nodules (6%). The mean age at presentation is 35 years (range 19 – 54 years). Pleural implants are found in less than 15% of patients at thoracic surgery. Diaphragmatic defects and/or parenchymal cysts or blebs occur in approximately 25% of cases.

Symptoms of thoracic endometriosis typically occur within 1 – 2 days of the onset of menses. The most common symptom is chest pain, which occurs in 90% of patients. Dyspnea is less frequent, occurring in about one-third of patients.

Several theories address the pathogenesis of endometriosis. The most popular hypothesis is that viable, benign endometrial glands and stroma reflux to the abdominal cavity during menstruation through the fallopian tubes, implanting outside the uterus (4), and fail to be cleared from the peritoneal cavity, via normal mechanisms (1, 5). Endometrial tissue can then move into the thoracic cavity, either through congenital defects in the diaphragm — more commonly found on the right side (6 – 10) — and/or through microembolization through the pelvic veins (11 – 13).

Obstetrical and gynecological procedures that disrupt endometrial blood vessels and lymphatics may allow lymphovascular entry of endometrial tissue. This observation is linked with the common association of pulmonary endometriosis and certain forms of endometrial trauma. Our patient had had an induced abortion 3 years before the onset of hemoptysis.

Thoracic endometriosis should be suspected when a woman of child-bearing age presents with recurrent episodes of chest pain, pneumothorax or hemoptysis. It may be difficult to confirm the diagnosis histologically by demonstrating endometrial tissue in the lungs. However, the diagnosis can be made by pleural fluid cytology or needle aspiration of lung masses, or from cytology specimens from bronchoalveolar lavage (14, 15). The diagnosis is usually established on clinical grounds, but is often delayed because the temporal association of symptoms with menstruation may not be recognized or appreciated.

The chest x-ray in pulmonary endometriosis is often normal. CT scanning reveals ill-defined local infiltrates, well-defined nodular densities and cystic lesions which may change in size during the menstrual cycle (16). Magnetic resonance imaging (MRI) is superior to CT in detecting pulmonary endometriosis (3). Bronchoscopic examination of the airways often reveals normal findings, but in rare instances endometrial tissue may be seen on endobronchial biopsy. Angiography is of little value in establishing the diagnosis (17).

Treatment of pulmonary endometriosis aims at abolishing or suppressing the endometrial tissue and preventing further pelvic seeding. Medical treatment, when effective, supports the diagnosis if pathologic confirmation of endometriosis cannot be obtained. Medical therapy centers on suppressing the function of the ectopic endometrium by disrupting ovarian estrogen secretion. Agents such as oral contraceptives, progestin, danazol or gonadotropin-releasing hormone agonists can be used therapeutically (3, 18). However, recurrence rates greater than 50% have been reported with hormonal therapy (18), due to incomplete suppression of ectopic foci and the possibility of perpetual pelvic seeding. Chemical pleurodesis is effective in preventing catamenial pneumothorax and hemothorax. Pleurodesis can be achieved via tube thoracostomy and the application of talc, or with surgical procedures utilizing pleural abrasion and partial pleurectomy with or without talc. Monthly chest pain may persist even after pleurodesis. Pelvic symptoms which are unresponsive to hormonal manipulation can be treated with gynecologic surgery, including hysterectomy with bilateral salpingo-oophorectomy. However, there may be recurrences if estrogen replacement therapy is used postoperatively, since it may reactivate quiescent thoracic endometrial tissue implants (19–22).

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Women at High Risk for Breast Cancer:

Preventive Strategies

George H. Sakorafas, M.D., Ph.D.

Abstract

Prevention of breast cancer is a high priority for women at risk for the disease. Management options for this group include close surveillance, chemoprevention, and prophylactic mastectomy (surgical prophylaxis). The optimal method remains to be determined. However, at the present time, close surveillance, which include breast self-examination, annual or semiannual physical examinations, and annual mammography starting at age 30, remains the most widely accepted method.

Key Words: Breast cancer, surveillance, chemoprevention, prophylactic mastectomy.

Introduction

BREAST CANCER IS THE MOST COMMON cancer among women, with the exception of skin cancer. It was estimated that almost 175,000 new cases woul be diagnosed in the United States in 1999 (1). Despite diagnostic and therdapeutic advances, about one-fourth of these women will die of the disease. This underscores the limitations of current approaches to breast cancer diagnosis and treatment, and emphasizes the need for prevention of this potentially lethal disease, at least for women in the high-risk groups.

Defining the "High-Risk Group" for Breast Cancer

Breast carcinogenesis is a multistep, multifactorial process. Both endogenous and exogenous factors are involved in this phenomenon and contribute to breast cancer risk. Recognizing these factors and identifying precancerous lesions are of crucial importance for developing effective preventive strategies. Recent progress in molecular biology and human genetics, and accurate estimation of the cancer risk in benign breast disease have enabled a more logical approach to the management of women at high risk. Clearly, defining "high risk" is the first significant step toward effective prevention. Family history is the most widely recognized risk factor for breast cancer development. Most women with a family history of breast cancer do not have the genetically transmitted form of the disease, and, therefore, their risk is much less. While this risk increases as the number of relatives with breast cancer increases, it rarely exceeds 30% (2). About 5 – 10% of breast cancers are due to a specific inherited mutation, most frequently *BRCA1* or *BRCA2* mutation, that confers an extremely high risk of developing breast cancer (ranging from 40 – 85%, depending on the population) (3 – 5). Proliferative lesions of the breast are associated with a modest (1.5- to 2-fold) increase in risk. Atypical hyperplasia is associated with a 4- to 5-fold increase in breast cancer risk (6). In the presence of other risk factors, the cumulative risk is further increased. For example, women having atypical hyperplasia and a first-degree relative with breast cancer have an 11-fold increase in risk over those without proliferative atypical changes (6). In contrast, non-proliferative lesions carry no increased risk of developing into invasive cancer. Lobular and ductal carcinoma *in situ* (LCIS and DCIS, respectively) are also associated with an increased risk. LCIS is associated with a 7- to 12-fold increase in risk and is considered a "marker" rather than an anatomical precursor of invasive carcinoma. In contrast, DCIS is an "anatomic precursor" of invasive breast cancer (7, 8). Finally, women with a prior history of breast cancer are at an increased (5-fold) risk for developing cancer in the contralateral breast; this risk is about 1% per year of survival and is significantly increased in the presence of other associated risk factors, such as hereditary or familiar breast cancer and atypical proliferative changes in the remaining breast (2).

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To help increase the accuracy of breast cancer risk estimates, Gail et al. proposed, in 1989, a tool based on the number of first-degree relatives with breast cancer, the age at first live birth, the age at menarche, the number of breast biopsies, and a history of atypical hyperplasia (9). The relative risk for each of these factors is multiplied to provide a composite risk (i.e., the Gail model). Women are considered to have a "high" risk for breast cancer when their risk is equal to or greater than that of the average 60-year-old woman. While the Gail model may be useful in predicting numbers of breast cancer cases in specific risk factor strata, it has only modest discriminatory accuracy at the individual level (10). This finding has obvious implications for use in clinical counseling of individual women.

Management Options for the High-Risk Group

Three options are available in the health care management of high-risk women (Table 1):

Surveillance

The majority of these women will choose the option of surveillance, which includes monthly breast self-examination, annual or semiannual physical examination, and annual mammography, starting at age 30 (11). Because of safety concerns relating to repeated radiation exposure starting at a relatively young age, breast ultrasonography may be a valuable alternative method for breast imaging in these women. The rationale for surveillance is early detection of breast cancer — if it develops — resulting in a much better prognosis.

TABLE 1
Women at High Risk for Breast Cancer: Management Options

- Surveillance
  - Breast self-examination (monthly)
  - Physical breast examination (annually or semiannually)
  - Mammography (annually)
  - Breast ultrasonography
- Chemoprevention
- Prophylactic mastectomy (total mastectomy)

Chemoprevention

Chemoprevention, mainly using tamoxifen, has been shown to be an effective method for primary prevention of breast cancer. The NSABP P-1 project found that tamoxifen reduced the risk of invasive cancer by 49% during a median follow-up period of 55 months (12). This conclusion is in contrast with the recent interim reports of two European trials (13, 14). However, the larger number of patients in the NSABP P-1 and its prohibition of hormone-replacement therapy among participants add to the strength of its findings.

Based on the results of this study, tamoxifen has been approved in the U.S. for reduction of breast cancer risk in women at high risk for this disease. However, chemoprevention by the use of tamoxifen should be considered only for women at increased risk based on National Cancer Institute criteria (Table 2) (9, 15). This therapy should be continued for five years. The relative benefit of tamoxifen for women on hormone-replacement therapy and for those with specific breast cancer genotypes remains to be determined. Long-term side effects of tamoxifen include endometrial cancer, stroke, pulmonary embolism, and deep venous thrombosis, particularly in women 50 years of age or older. However, tamoxifen is also associated with some beneficial side effects, including a reduction in hip, radius, and spine fractures, probably due to the maintenance of bone mineral density. Interestingly, in a recent study, the risk of invasive breast cancer was decreased by 76% during three years of treatment with raloxifene — another antiestrogen — among postmenopausal women with osteoporosis (16). Of note, in this study the use of raloxifene has not been associated with an increased risk of invasive uterine cancer. The effectiveness of chemoprevention by the use of tamoxifen and raloxifene is currently being evaluated in an ongoing trial (STAR trial; Study of Tamoxifen and Raloxifene).

TABLE 2
Factors Used to Determine the Risk of Breast Cancer

- Age
- Race
- Age at menarche
- Age at first live birth
- Number of breast biopsies
- Atypical hyperplasia
- Number of first-degree relatives with breast cancer

Surgical Prophylaxis (Prophylactic Mastectomy)

Surgical prophylaxis (prophylactic mastectomy) is another option for primary prevention of breast cancer. However, prophylactic mastectomy is considered too drastic an option, especially in an era of breast conservation therapy, in which one breast with cancer is preserved (albeit irradiated), while two normal breasts are amputated in the name of "prophylaxis." Existing data suggest that prophylactic total mastectomy significantly reduces (by ~ 90%), but does not totally eliminate, the risk of subsequent cancer development, probably from the residual amount of breast tissue that remains after prophylactic mastectomy. This is the "Achilles' heel" of surgical prophylaxis. Survival improves by 2.8 – 6 years over surveillance alone (17 – 20).

At present, prophylactic mastectomy should be considered only for a relatively small number of carefully selected patients. The decision to perform a prophylactic mastectomy should be a multidisciplinary one and must be based on the objective risk for breast cancer development, the woman's personal values and experiences within her family, and her concerns about developing breast cancer. Detailed patient counseling is very important and the patient should understand the limitations of prophylactic mastectomy, the irreversibility of the decision, and the need for postoperative follow-up. Furthermore, she should be well informed about the alternative strategies.

The role of diet in the development of cancer (including breast cancer) has been evaluated in many epidemiological studies. However, although diet may have an impact on breast cancer risk, dietary modification alone is not likely to be sufficient to prevent breast cancer (21).

No data exist comparing prophylactic mastectomy vs. surveillance vs. chemoprevention. Thus, despite significant advances in our understanding of the biology of breast cancer, many questions remain concerning the optimal health care management of high-risk women. Patient counseling has a central role in the decision-making process and should be based on a multidisciplinary approach. The individual woman will make the final decision, according to the amount of risk she is willing to accept. For the future, other preventive methods may become available which will more accurately estimate the risks associated with developing breast cancer.

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Medicine on the Internet:

Jewish Perspectives

FRED ROSNER, M.D.

Abstract

The ethical principles of beneficence and non-maleficence are deeply rooted in Judaism. A physician is obligated to heal and is given Divine license to do so. A patient is also obligated to seek healing.

Judaism also emphasizes prevention over treatment. Avoidance of danger and thereby the preservation of life and health are biblical mandates. Rules of personal hygiene such as hand washing before eating are also stressed, as are diet, exercise, and general care of the body. Preventive medical services and patient responsibilities are fully in accord with Jewish thought.

Specifically with regard to the internet, Judaism views any new technology or scientific advance with favor if it is used for the betterment of mankind, such as the prevention and treatment of illness. The internet is a wonderful tool to accomplish this purpose. It can promote health education to millions of people and thereby help to prevent illness. It can be used to facilitate communication not only between physicians and patients, but between health care providers and large population groups. All these goals are consonant with traditional Jewish thought and practice.

However, potential negative consequences from the medical use of the internet must be considered and avoided. Misleading or false medical information should be weeded out. Inappropriate medical commercialism on the internet should be banned. Confidentiality of medical information must be preserved. The limitations of the internet for the practice of medicine (e.g., lack of personal patient-physician contact) should be clearly explained to patients, to help them appreciate those features of the internet which can truly benefit them and society.

Key Words: Internet, Jewish perspectives, medical practice.

Background

ACCORDING TO DR. GEORGE LUNDBERG, former Editor-in-Chief of the *Journal of the American Medical Association* and presently Editor-in-Chief of *Medscape*, "The internet is the most significant advance in human communications since the printing press. It is going to change the face of how humans interact in almost every realm, including the way medicine is practiced" (1).

Physicians are increasingly using the internet to improve the flow of information, increase transaction efficiencies, including electronic billing, enhance patient recruitment and satisfaction, provide patient education, verify patients' health care coverage and, in general, capture the attention of health care consumers online. And patients are using the internet to learn more about their health care needs, form and join health care support groups, and become more sophisticated health care consumers.

The control of online health information is being pursued by physicians, hospitals, insurance companies and other "players" in the health care field. The American Medical Association and six other medical societies have created Medem Inc. (www.medem.com), a for-profit venture which provides physicians with individual websites containing state-of-the-art, peer-reviewed consumer health information. Other well-respected health care information websites are Health Oasis, run by the Mayo Clinic (**www.mayohealth.org**) and InteliHealth (**www.intelihealth.com)**, a for-profit partnership between the Johns Hopkins Medical Center and Aetna U.S. Healthcare. Medscape Inc. (**www.medscape.com**) is allied with CBS News, while Healtheon/WebMD (**www.webmd.com**) is partnered with both CNN and News Corporation.

Unfortunately, this electronic "health commerce" is associated with many ethical and legal problems. Conflicts of interest and nondisclosure of vital commercial links were highlighted in regard to the Dr. Koop.com website (www.drkoop.com). Dr. Koop failed to disclose that he had received commissions on products sold, as well as for patients recruited for clinical trials, through his website. Hospitals listed as "innovative" paid $40,000 each for that endorsement.

The quality of the health care information on many websites is open to serious question. Health cures are being offered that are "too

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good to be true." The magnitude of health care fraud over the internet is difficult to measure, but is certainly in the billions of dollars. Unproven and/or ineffective treatments for a variety of ailments are widely promoted and sold over the internet (see quackwatch.com). Although the internet hosts a large number of high quality medical information sites with great potential to inform patients and physicians alike, "The problem is not too little information but too much, vast chunks of it incomplete, misleading or inaccurate" (2). Most medical information directed at the lay public on the internet is unchecked, unstructured and unregulated.

The American Medical Association (AMA) recognized the wide variations in quality of content on the Web, the potential for commercial interests to influence online content, and the risks to personal privacy. As a result, the AMA developed and promulgated principles to guide development and posting of website content, govern acquisition and posting of online advertising and sponsorship, ensure site visitors' and patients' rights to privacy and confidentiality, and provide effective and secure means of e-commerce (3). About the same time, Medscape established principles governing the acceptance and display of advertising on its website (4).

To help ensure the ethical content of internet information, an international nonprofit organization called the Internet Healthcare Coalition (IHC) was formed, dedicated to quality health care resources on the internet. The IHC, in collaboration with the Hastings Center for Ethics, was instrumental in drafting the International e-Health Code of Ethics (5). The code aims "to ensure that all people worldwide can confidently, and without risks, realize the full benefits of the internet to improve their health." The guiding principles involve candor and trustworthiness; quality; informed consent, privacy and confidentiality; best commercial practices; and best practices for provision of health care on the internet by health care professionals.

Physician-Patient Communication by E-Mail

Electronic mail between physicians and patients offers substantial promise as a way to improve access to health care, enable physicians to reach out to patients, and increase the involvement of patients in their own care (6). Elderly patients can consult their physicians by "electronic house call" to record their vital signs and discuss their condition (7). The installation of "telemedicine" equipment, including glucometers and blood pressure devices, in the homes of low income Medicare recipients living in medically underserved areas of New York State has been proposed. This proposal, if successfully implemented, could improve care and be cost effective, and could serve as a model for treating a wide range of conditions such as asthma, congestive heart failure, obesity, smoking addiction, and depression (8). Electronic prescribing systems might reduce prescription errors. Some state legislatures are considering bills to give consumers internet access to doctors' malpractice and disciplinary records. The possibilities of electronic medicine doctor-patient interaction seem limitless.

In its *Code of Medical Ethics*, the AMA advises physicians about telecommunication (phone, fax or computer) contacts with patients (9). Diagnosis by telecommunication is done without the benefit of a physician examination or even a face-to-face meeting with the patient. Critical medical data may be unavailable to the physician, whose response must thereby be limited and perhaps inconclusive. The confidentiality of computerized medical records must be protected. In addition, the AMA has promulgated guidelines for the clinical use of electronic mail with patients (10). The guidelines address two interrelated aspects: effective interaction between the clinician and patient and observance of medicolegal prudence. Prescription refills, lab results, appointment scheduling and reminders, insurance questions, routine follow-up inquiries, and reporting of home health measurements such as blood pressure and glucose are all well suited to e-mail. Highly confidential information or medically urgent or emergent situations should not be communicated by e-mail.

Medicolegal and administrative guidelines are also provided in the AMA's Task Force Report (10). Legal issues concerning electronic health information include the privacy of identifiable health information, the quality and reliability of health data, and tort-based liability (11). Recommendations for legal reform include recognizing identifiable health information as highly sensitive, providing privacy safeguards, empowering patients with rights to consent to disclosure, limiting disclosures of health data without consent, incorporating industry-wide security protections, and more (11).

The California Health Care Foundation surveyed over a thousand average American internet users and found that most users are concerned about the privacy of on-line health information, suspicious of the ethics of many internet health websites, uncertain whether personal health data are protected by law, and confused about who should regulate internet health information or if it should be regulated (12).

To satisfy the needs of patients, physicians and society as a whole, the following conclusions seem to be appropriate:

> policy or legislative initiatives for medical records privacy and health information security should explicitly address patient-centered communication with health care professionals and require that patient autonomy, safety and privacy be maintained when the patient-physician relationship is electronically extended or enhanced. In turn, policymakers should ensure that physicians apprise patients of the privacy implications and inherent risks of e-mail communication as part of an informed e-mail consent process, to be finalized by a signed written consent form. Further, policymakers, physicians and patients should recognize that transcripts of electronic medical communications become part of patients' medical records, and therefore deserve the privacy and confidentiality protections afforded to all medical records (13).

Jewish Issues

Is there anything Jewish or un-Jewish about the internet? Does the Torah permit, mandate or prohibit use of the internet? In January 2000, a group of Orthodox Israeli rabbis issued a ruling exhorting Jews to remove the internet from their homes, although the rabbis acknowledged its great value in the workplace. One of the major concerns of the rabbis is the problem of young people accessing pornographic sites and using chat rooms to communicate with unsavory characters. The dangers of the internet, like those of television, movies, theater and many newspapers and magazines, in the opinion of these rabbis, outweigh its value in the home.

Yet the pursuit of knowledge and the proper use of new technology and scientific advances are certainly not prohibited in the Torah. On the contrary, no less a person than King David supported the concept that knowledge and its pursuit and application are legitimate activities for human beings and are not considered an encroachment upon Divine prerogatives when he wrote, "The heavens are the Lord's heavens, but the earth He has given to mankind" (Psalms 115:16).

The pursuit of knowledge in medicine is exemplified in the therapeutic possibilities offered by genetic engineering, gene therapy and cloning. The genome project is not an encroachment on the Divine plan for this world. It does not interfere with nature as God created it. It does not tamper with the Divine arrangement of creation. God blessed mankind with the phrase, "replenish the earth and subdue it" (Genesis 1:28). This phrase is interpreted by Nachmanides (Ramban) to mean that God gave man dominion over the world to use animals and insects and all creeping things for the benefit of mankind (Ramban, Genesis 1:28). To subdue the earth, according to Samson Raphael Hirsch (Hirsch, Genesis 1:28), is to master, appropriate, and transform the earth and its products for human purposes. To have "dominion over the fish and over the birds and over every living thing on earth" (Genesis 1:28) means to use them for the benefit of mankind. The pursuit of scientific knowledge does not constitute prohibited eating from the tree of knowledge (Genesis 2:17). Whatever is good for mankind must be permissible and praiseworthy.

However, good often is not pure good, but may contain potentially dangerous elements. The genome project is intended to cure diseases, but has raised many ethical, legal and social concerns (14). Similarly, the internet is a wonderful scientific and technological advance, with enormous beneficial potential for mankind. Its use must certainly be sanctioned in Jewish law. However, Jewish concerns about potential dangers of the indiscriminate use of the internet must be addressed. Pornographic and other prurient and/or defamatory material must be blocked out by Jewish users, to avoid violating the biblical and rabbinic laws concerning immorality. The placing of misleading or potentially harmful information, medical or otherwise, violates the prohibitions against deception (Chullin 94a) and (metaphorically) against placing a stumbling block before the blind (Leviticus 19:14) or leading the blind astray (Deuteronomy 27:18). The addictive qualities of the internet result in sleep deprivation for many people who spend more time online than they intended. Such addiction may take its toll on one's health, school grades, employment, marriage, Torah study, etc.

Some people advocate government supervision or regulation of the internet. Others respond that such regulation violates the U.S. Constitution. How can a website which screens out pornographic material in order to protect children at the same time retain beneficial information for discerning adults? There already exists a website, Koshernet.com, which tries to address these issues. We can benefit from the internet in terms of learning Torah, obtaining Jewish and Israeli news, conducting electronic correspondence and commerce, and carrying out other beneficial activities. However, restrictions and parental guidance are needed to avoid undesirable sites and prevent "electronic addiction." Fascination with the internet may interfere with other Jewish pursuits and necessities, so that moderation is needed. Guidelines have been suggested for the Jewish home (15), to avoid the tangled web (16) and the landmines along the information highway (17).

Medicine on the Internet

In the field of medicine, the internet could serve to provide health information to very large audiences. Judaism requires communities to not only provide for the medical and social needs of their citizens, but also alert people about drug recalls, epidemics and the dangers of substance abuse. Judaism thus encourages modern technology to be used for the benefit of mankind.

The practice of medicine over the internet is a multifaceted issue. The basic principles in Judaism governing the practice of medicine, whether in the doctor's office, over the telephone or on the internet, are based on the premise that a physician is given specific Divine license to practice medicine. The biblical verse "and heal he shall heal" (Exodus 21:19) is interpreted by the talmudic sages (Baba Kamma 85a) to mean that authorization is granted by God to the physician to heal (18, 19).

An axiom of Judaism is that human life is of infinite value. The preservation of human life takes precedence over all commandments in the Bible except those prohibiting idolatry, murder and forbidden sexual relations. Life's value is nearly absolute and supreme. In order to preserve a human life, the Sabbath and even the Day of Atonement may be violated, and all other rules and laws save the aforementioned three are suspended for the overriding consideration of saving a human life. He who saves one life is as if he saved a whole world (Sanhedrin 37a). Even a few moments of life are worthwhile.

These Judaic principles, therefore, require that physicians place the interests of their patients first and advocate for any care they believe will materially benefit their patients. Physicians must practice good medicine, eliminate that which is unnecessary, and be aware of the need to contain costs. Physicians must also practice within the areas that they are credentialed, and do so in the best interests of their patients.

A physician is entitled to reasonable fees and compensation for his services (20). Indigent patients, however, should be treated for reduced fees or no fees at all.

With the ever-expanding use of the internet for medically related issues, there are concerns regarding the extent to which physicians should use it to provide care for individual patients. For example, certain neurological and dermatological conditions might be evaluated by a consulting physician via telemedicine. The consultant could suggest further diagnostic and therapeutic strategies by e-mail. Patients, their families and their health care providers in remote locations might be able to communicate with a physician via the internet whenever an actual meeting is not possible or feasible. However, physicians should always strive to establish a direct patient relationship before providing medical care via the internet or e-mail. Furthermore, the internet should not be used for urgent or emergency medical conditions, except in the most unusual circumstances. Direct communication with the physician or ambulance service (#911) should then be used. Particular attention needs to be devoted to the confidentiality of medical information and direct patient-doctor communication via e-mail.

Physicians should be concerned about the use of e-mail communication with their patients because physicians are legally responsible for any advice or management provided via e-mail. Malpractice issues have not yet been fully explored regarding medicine practiced on the internet. For non-established patients, physicians usually avoid diagnosing and/or treating without first seeing the patient. As patient enthusiasm increases, however, more and more physicians will be called upon to render advice and provide medical information via electronic means, with appropriate attention to safeguarding confidentiality.

Preventive Medicine and the Internet

Government agencies, foundations, societies and universities are disseminating more information regarding healthcare concerns via the internet. The internet has the potential to inform people about healthy living and how to prevent illness, thus reducing the incidence of diseases and adverse events. For example, encouraging the cessation of smoking has been shown to reduce the risk of lung cancer. A variety of prevention strategies (e.g., aspirin, exercise, weight reduction, blood pressure and lipid control, etc.) can reduce the risk of a heart attack.

The prevention of illness and the avoidance of potential hazards are mandated in Jewish law. Preventive medicine has been the centerpiece of the Jewish system for more than two thousand years. The Jewish view emphasizes prevention over treatment.

An entire chapter in Moses Maimonides' famous *Mishneh Torah* (Code of Jewish Law) (21) is devoted to hygienic and medical prescriptions for healthy living and for the prevention of illness. Among the many subjects discussed are normal bodily excretory functions, recommended times for eating, amounts and types of food to be consumed, beverage consumption, exercise, sleep habits, cathartics, climatic and weather effects on eating habits, detrimental and beneficial foods, fruits, meats, vegetables, bathing, bloodletting, sexual intercourse, and household conditions.

He also discusses ecological and environmental factors that may impact on one's health, such as clean air and sunshine. Maimonides concludes his exposition as follows:

> I assure anyone who conducts himself according to the directions we have laid down that he will not be afflicted with illness all the days of his life, until he ages greatly and expires. He will not require a physician, and his body will be complete and remain healthy all his life unless his body was defective from the beginning of his creation, or unless he became accustomed to one of the bad habits from the onset of his youth, or unless the plague of pestilence or the plague of drought comes onto the world (21).

Maimonides cites exceptions to the goal of preventing rather than treating illness. Genetic diseases and certain epidemics of diseases cannot be prevented. For this reason, the final paragraph in Maimonides' chapter on the regimen of health states that a person should not reside in a city that does not have a physician. A similar pronouncement is found in the Talmud (Sanhedrin 17b). Maimonides supports the adage "An ounce of prevention is worth a pound of cure." Much more evidence for this thesis is found in his medical writings (22).

The internet is a technological device perfectly suited to provide preventive medicine information to huge numbers of people, to indoctrinate them in the benefits of healthy living, to teach them about the health risks of smoking and substance abuse, to encourage them to follow sensible and logical lifestyles, including proper diet, exercise, periodic health screenings, and to convince them of the benefits of preventing illness. Judaism views all these goals and objectives as laudatory. Possible liability issues, however, may require the physician and the internet service to be extremely cautious about providing medical information which might lead to unwanted or undesirable effects in some individuals.

Patient Responsibility

The Bible also tells us to "take heed to thyself, and take care of thy life" (Deuteronomy 4:9) and "take good care of your lives" (ibid. 4:15). These biblical mandates make it clear that patients are obligated to care for their health and life. Human beings do not have full title over their lives and bodies. They must eat and drink to sustain themselves and must seek healing when sick.

In the Western world, citizens are endowed with a variety of legal rights. People have the right to die, the right to refuse treatment, the right not to be resuscitated, the right to an abortion, and many others. Rarely does one hear about citizens' responsibilities and obligations. Judaism requires everyone to do what is proper in order to be healthy. It is an obligation in Judaism to be healthy. Hence one should accept appropriate medical advice, whether given in person, over the telephone, by fax, e-mail or over the internet. One should not smoke, one should eat properly and not excessively, one should exercise regularly, sleep adequately, only engage in proper and legitimate sexual activities, and lead an overall healthy lifestyle. These are moral obligations and legal imperatives in Judaism.

Thus, while much of the modern secular ethical system is based on rights, Judaism is an ethical system based on duties and responsibilities. Rabbi Lord Immanuel Jakobovits eloquently articulates the Jewish view as follows:

> Now in Judaism we know of no intrinsic rights. Indeed there is no word for rights in the very language of the Hebrew Bible and of the classic sources of Jewish law. In the moral vocabulary of the Jewish discipline of life we speak of human duties, not of human rights, of obligations, not entitlement. The Decalogue is a list of Ten Commandments, not a Bill of Human Rights (23).

Therefore, Jewish internet users may be obligated to use it to prevent and to treat illnesses. For some patients, the internet may be an absolute necessity. Patients with very rare conditions or diseases can communicate with physicians and experts and other patients, about their cases. Laypersons who need sources of help such as support groups, medical care and specialists can obtain such assistance and information on the internet.

Confidentiality and the Internet

Confidentiality of medical information is one of the major concerns relating to the internet. There are no major ethical difficulties if physicians provide general medical information on the internet. However, patients' private medical information transmitted by e-mail from patient to physician and vice-versa is accessible to many people with computer expertise, and therefore requires special and careful consideration. Patients must be told that the internet is not a secure means of communication, since internet messages can potentially be intercepted, viewed, and altered by unauthorized individuals. Items "deleted" may still be recoverable. Therefore, confidential information should not be sent over the internet.

Even clerical and administrative communications, such as billing, appointments and insurance matters, and all e-mail communications related to patient care should be considered sensitive and confidential. Patients must also consider the security of their own home or office computers in regard to the confidentiality of their medical information. The challenge to preserve confidentiality must be pursued and met by the adoption of secure means of data transmission.

The obligation to maintain confidentiality is one of the cornerstones of medical ethical practice and is clearly stated in the Oath of Hippocrates and subsequent professional oaths and declarations. It is based on the general ethical principles of doing good for others (beneficence), not to harm others (non-maleficence), patient autonomy, and the right to privacy. It is also based on the trusting relationship between patient and physician and the need to protect and preserve that relationship by not disclosing to others private and personal information about the patient.

Maintaining professional confidentiality is a subject which Jewish thought and literature have dealt with extensively over the centuries (24). In Judaism, the right of privacy must be balanced against the needs of society as a whole (25). Jewish law regards as inviolate the privacy of personal information that a person does not wish to disclose to others. It demands that confidences be respected, not only by professionals with whom one has entered into a fiduciary relationship, but also by friends and acquaintances and even strangers to whom such information has been imparted (26). The obligation of confidentiality in Judaism is far broader than that of any other legal, religious, or moral system, but "is neither all-encompassing in scope nor, when it does exist, is it absolute in nature" (27).

There is no specific term in Jewish law for professional confidentiality, since this topic is subsumed under the general prohibition against talebearing and evil gossip (Leviticus 19:16; Proverbs 25:9; Psalms 34:14). The prohibition against divulging confidential information is discussed in the Talmud (Yoma 4b), which states that if a man says something to his neighbor, the latter is not allowed to repeat it without the man's specific consent. This conclusion is based on a biblical verse (Leviticus 1:1). Another talmudic discussion of confidentiality (Sanhedrin 31a) states that judges may not reveal confidential discussions that take place behind closed doors. The prohibition against talebearing (Leviticus 19:16; Proverbs 11:13) is here interpreted to include revealing secrets even if the information is true and no harm is meant. The Talmud also indicates that this prohibition has no statute of limitations. A scholar was rebuked for having revealed a secret after twenty-two years (Sanhedrin 31a). The biblical prohibitions against talebearing and gossip are codified by Maimonides in his *Mishneh Torah* (*Deot* 7:2).

According to these laws, a physician may not share privileged information with his colleagues, his family, or anyone else if no benefit to the patient would result therefrom (28). However, if the maintenance of confidence might cause harm to another person, the latter may be informed. If the individual's right to privacy conflicts with the need of society to prevent harm to others, the prohibitions against talebearing and evil gossip are waived and the information must be disclosed to protect other people. The disclosure must be factual, accurate and not exaggerated.

Specific medical situations where disclosure is required include the possible transmission of disease to another person, the presence of a serious medical condition in a potential spouse, and the reporting of certain infectious diseases to public health authorities. The overriding obligation to protect the lives of others requires that confidential information be disclosed if the withholding of that information might lead to serious harm to someone else. Judaism thus balances the obligation and duty to maintain confidentiality with the obligation and duty to protect others. Detailed discussions of this topic are available elsewhere (21–25).

Summary and Conclusion

The attitude toward healing in Judaism has always been a positive one. A physician is obligated to heal and is given Divine license to do so. A physician must be well trained and licensed in his discipline. A physician must apply his skills for the benefit of the patient and be careful not to do harm. Thus, the ethical principles of beneficence and non-maleficence are deeply rooted in Judaism. A patient is also obligated to seek healing, since one must be healthy in order to serve the Lord by doing His will in the service of mankind.

A second cardinal principle of Judaism is the infinite value of human life. The preservation of life takes precedence over all biblical and rabbinic commandments except those prohibiting murder, idolatry and forbidden sexual relations such as incest or adultery. The Talmud states that all lives are equal, since one person's blood is not redder than that of another (Pesachim 25b).

Preventive medicine is a centerpiece of the Jewish system. The Jewish view of medicine emphasizes prevention over treatment. Prevention of danger and thereby the preservation of life and health are biblical mandates. One must observe rules of personal hygiene such as handwashing before eating. Diet, exercise, sex and bodily functions must all be properly tended to. Preventive medical services and patient responsibilities are fully consonant with Judaism. Thus, emphasis on prevention of illness, as well as personal responsibility, are deeply rooted in Judaic teaching and tradition.

Specifically with regard to the internet, Judaism views any new technology or scientific advance with favor if it is used for the betterment of mankind, such as the prevention and treatment of illness. Such harnessing of the natural sciences is not considered an encroachment upon Divine prerogatives. On the contrary, God gave us dominion over the world to use nature to subdue the earth (Genesis 1:28); this includes transforming its secrets into products and technology to benefit mankind.

The internet is a wonderful tool to accomplish this purpose. It can educate millions of people about preventing illness. It can be used to facilitate communication between physician and patient. It can be used to reduce prescription and other errors caused by physicians' illegible handwriting. It can contribute to the good health not only of individual patients but of whole societies and large population groups. All these goals are consonant with traditional Judaic thought and practice.

However, potential adverse aspects of the use of the internet for medical purposes must be considered and avoided. Misleading or false medical information must be weeded out. Inappropriate medical commercialism on the internet must be banned. Confidentiality of medical information, even with the informed consent of the individual patient, must be preserved unless there is an overriding lifesaving reason to do otherwise. The limitations of the internet in the practice of medicine by e-mail (e.g., lack of personal patient-physician contact) must be clearly explained to patients, to allow them to maximize the use of the internet for their personal and medical benefit.

Finally, the internet should serve to foster continuing professional medical education of physicians and health care providers, and to enhance information exchange among professional colleagues.

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Commencement Address—2002

Science and Humanism:

The Twin Pillars of Medicine

Barry S. Coller, M.D.

I want to thank the class of 2002 for the honor of addressing you today. I have the awesome responsibility of providing you with wise and inspiring words that will guide your entire future life, but I am comforted by knowing that I can't remember a single word of the commencement address when I graduated from medical school, or even who gave the address! To give you some idea of how dangerous it can be to offer advice that you expect to survive the ages, I need only quote from the 1938 commencement address of Dr. Rufus Cole, a protégé of the great Sir William Osler (1):

> During your intern days the hospital should be your home, your workshop, and your playground, you should need nothing more. Learn to shun outside affairs that will complicate your life . . . rejoice if you are too poor to own an automobile . . . avoid the movies, you will find sufficient tragedy as well as comedy close at hand. . . . above all, avoid like the plague entangling affairs of the heart. . . . I am still convinced of the soundness of Dr. Osler's advice to 'put your affections in cold storage during your intern years.'

We are here today to pause briefly from our usual daily work to celebrate achievement; to reflect on the past; and to prepare for the future. So let us savor this precious moment.

First and foremost we are here to celebrate your individual achievements as some of you receive your master's degrees in genetic counseling and community medicine, others your doctoral degrees in biomedical sciences, and still others your doctor of medicine degrees. Each of you has demonstrated nearly superhuman self-discipline and made many sacrifices to prepare yourself for this very moment, which marks the beginning of your professional career in the healing arts. And your reward is the life-long blessing of being able to apply your unique intellectual gifts and humane insights to prevent and alleviate suffering from illness. At a time when the forces of hate and destruction are directly threatening the single core value that defines our civilization, namely the preciousness of each human life, you have chosen to devote yourselves to preserving that value with all your heart, your brain, and your soul. You should feel very good indeed, about your choice, yourself, and your calling.

This is also a time to give thanks to all your loved ones, those who could be here today and those who could not. They also made sacrifices to help you achieve this goal in your lives. Those who are closest to you and share your daily life know how difficult some days can be for you. Their encouragement, understanding, good humor, and belief in the importance of what you are doing, serve as a vital refuge against a tough and increasingly unforgiving world. For many of your parents and grandparents this day symbolizes the fulfillment of their hopes and dreams for you — and vows they made to you when you were still in their arms.

This is also a time for you to reflect on the great legacies of The Mount Sinai Hospital and the Mount Sinai School of Medicine, and to thank the extraordinary faculty of physicians and scientists who have taught you about the wonders of the human body and the majesty of the human spirit. Their devotion to teaching reflects one of the highest values of our calling, the seamless transfer of medical knowledge and medical professionalism to the next generation of physicians and scientists. As the fire from a single candle can light many others, so have they inspired you to relish the thrill of discovery and to appreciate the awesome human re-

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The following address was delivered to the Mount Sinai School of Medicine, Class of 2002 on May 10, 2002.

sponsibilities that come with being a member of the health professions. I would suggest that the very best way to thank them is by making your own broad commitment to be a teacher, role model, and mentor for those who follow you, starting with elementary and high school students who are considering careers in health-related disciplines, especially those from disadvantaged backgrounds. This will not only ensure a continuous flow of outstanding young people into medicine, but also provide you with an unmatched sense of fulfillment and purpose.

One hundred and fifty years ago a visionary group of men and women, motivated by the moral imperatives of the Jewish religion to help those in need, gave generously of their time and resources to establish the first hospital in New York that would care for Jews who lacked the means to pay for their care. When that need was met, they expanded their commitment to include all those who were ill, regardless of race, religion, or ability to pay. That commitment, not bricks and mortar, is the true cornerstone of The Mount Sinai Hospital, and it has lived on as the institution's guiding philosophy through many generations. As you undoubtedly sense, however, despite the loyalty, devotion, and generosity of our trustees and many other supporters, the current financial realities facing all teaching hospitals that cherish community service, threaten to make it impossible to sustain that commitment. So I encourage you to be inspired by Mount Sinai's legacy and its leaders, and advocate for those most in need. Do not rest until high quality health care is considered a right of every person in this country and around the world.

What makes medicine both uniquely challenging and rewarding is that it stands atop the twin pillars of science and humanism, requiring the integration of these disciplines in the service of humankind. The expert physician has a comprehensive and deep scientific understanding of the causes of illness and the rational basis of disease prevention and therapy; the compassionate physician applies that knowledge with sensitivity to the unique needs and circumstances of a single complex individual. As a scientist, one resists accepting a new theory until the data are absolutely compelling, whereas as a physician one must act on incomplete evidence because the patient needs treatment now; as a scientist one looks for those elements that are common to a series of observations, and thus generalizable, whereas as a physician one seeks out that which is special or different about one's patients; and as a scientist one will go to extraordinary lengths to eliminate all variables except the one under study, whereas as a physician, one can rest assured that the patient who sits before you is never exactly as depicted in the textbook. It is worthwhile to reflect, therefore, on the benefits that both science and humanism, each with its own perspective and values, can bring to individual patients and the public good.

The power of science is truly awesome. It is responsible for increasing the lifespan of humans during the past 150 years since the founding of this institution as much as had been achieved in the previous 3000 years. And the pace of new scientific discovery continues to escalate as the tools of science improve and as the resources society commits to science increase. The National Institutes of Health, which are funded by the federal government, have doubled their support of medical research during the past five years, and similar increases in support have come from the pharmaceutical and biotechnology industries. One graphic statistic is the estimate that as many as one-half the scientists that ever lived are currently alive, and I wouldn't be surprised if this was an underestimate in biomedical research.

The advances in medical science since I graduated from medical school 32 years ago are truly breathtaking and awe-inspiring. At that time, not a single gene had been cloned or sequenced, and the ongoing international race was to break the triplet code that converts genetic letters into genetic words. Now virtually all of our more than 30,000 genes have been sequenced. Equally staggering, in 1970 we did not have even one of the crucial tools we now take for granted to translate new genetic and biochemical information into new therapeutic advances — monoclonal antibodies, recombinant proteins, synthetic peptides, combinatorial chemistry, proteomics, and high throughput robotic screening. Stem cells were the province of a handful of theoretical biologists, not on the front page of every newspaper. Coronary artery angioplasty, which is now performed on approximately 3,000 patients every day in the United States, was still almost a decade away from being invented, and the idea of a coronary artery stent would have likely provoked dismissive and derisive laughter. Renal dialysis and kidney transplantation were just beginning and seemed miraculous, but we had nothing to offer those who needed a new bone marrow, a new liver, or a new heart.

Harnessing the power of the scientific method to alleviate suffering from disease is one of humankind's proudest achievements. And while all discoveries are intellectually thrilling as they reveal yet more information about us and our world, those discoveries that have the potential to heal have an added, even spiritual, dimension. Some of you will have the unique satisfaction that comes from devoting all of your energies to help build the pillar of medical science taller and stronger, but I encourage each of you to think of yourselves as scientists as you apply the scientific method to your chosen discipline, whether it be medical education, biomedical ethics, or primary patient care. The first clinicians to report patients suffering from AIDS, West Nile virus, and anthrax were great scientists.

But what of that other pillar — the pillar of humanism? Given the complexity and diversity of the human experience, given the differences in human culture, history, religion, values, priorities, and assumptions about life, how can we ever hope to keep building it taller and stronger so that it continues to match the progress of the pillar of medical science? For to allow medical science to outstrip medical humanism poses as great a threat to us as to stop medical science itself. This is the monumental task before you, the graduates, and before all of us assembled today. Since I have no grand scheme or simple answers, allow me rather to share some humble thoughts.

The core of medical humanism is equal respect for all human life. Compassionate physicians never lose their sense of awe for the miracle of life and they recognize the common humanity they share with each of their patients. To paraphrase the physician's prayer ascribed to the great Jewish physician, Maimonides, which you will read shortly, the physician should not consider the patient "a vessel of disease" but rather a fellow human who is suffering. It is natural that physicians, especially when training, increasingly view the physician-patient relationship from the physician's perspective. However, when you view the relationship from your patients' perspective and the perspectives of their loved ones, you will realize that your patients' fears and hopes are profoundly affected by everything you say and how you say it. The words you speak during your daily hospital room visit will be analyzed over and over again by your patients and their families, so you must choose those words with care and you must deliver them with sensitivity. Eight years ago, Elie Wiesel (2) told the graduating class of this great school that "no one is as defenseless, as disarmed, as a person in pain and devoured by anguish. He or she will study every line in your face, every word on your lips. At that moment, you personify either hope or despair." He went on to say that "no one is as grateful as the patient who discovers a ray of hope in the eyes of his or her physician." So I encourage you to think hard about what your eyes are conveying to your patients. Art, literature, poetry, theater, and cinema can be great aids to help you keep the patient's perspective before your eyes, but nothing is as good as really listening to your own patients, sympathetically hearing their life story, and learning what they have to teach you. And nothing is as rewarding.

Finally, I believe that it is an understanding and appreciation of the importance of human diversity that lies at the center of humanism. In fact, because of the vagaries of the history of our species and the treacherous population bottlenecks that only the heartiest, or perhaps the sexiest, of our ancestors were able to squeeze through, we have dangerously little genetic diversity. Current estimates from the genome project are that humans of all races vary from each other by only about one ten-thousandth in their genetic makeup. Our genetic uniformity actually presents a serious risk, since we have learned from population genetics that our ability to survive the assaults that threaten our species on a daily basis, whether HIV or other scourges, depends on our having sufficient molecular diversity so that at least some of us survive. The case of HIV is most informative, since recent evidence demonstrates that having a rare mutation in a chemokine receptor needed for the entry of some HIV viruses into cells can protect a person from getting infected. Today's scorned "mutation" can thus be the key to saving our species tomorrow. Now, that is a reason enough to celebrate diversity. But there are many more reasons, since by respectfully learning from people who see and do things differently, we enrich each other, broaden each other's vistas, and give meaning and texture to each other's lives. In fact, the very best way to learn about ourselves is by seeing the choices that others have made. We are assembled here today in New York City, which has become the undeclared capital of the world precisely because it is the most diverse city in the world. Never forget that the sparks of creativity are always the brightest and most intense when powerful cultures and ideas meet head on.

And so, as you begin your careers today, I encourage you to go forward with confidence and self-assurance, knowing that you have received a superb education from many of the greatest physicians and scientists of our age, and from a concerned and caring institution that serves the most diverse population of patients in the world in the greatest city in the world. You are truly well prepared for your task. You will succeed.

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Irving L. Schwartz Lecture

Pathogenesis and Prediction of Diabetes Mellitus:

Lessons from Integrative Physiology

Richard N. Bergman, Ph.D.

Abstract

The molecular revolution in biology is providing an exponentially increasing body of data regarding subcellular events in normal and pathological conditions. The task of integrating even a small part of this deluge of information is a formidable challenge. Many integrative regulatory principles are still unknown. The present article argues that important principles may be discovered by the repetitive experimental testing of simple isomorphic computer or mathematical models of biological regulation. The system regulating the blood glucose is used as an example. Implicit in a "minimal model," postulated more than 20 years ago, were specific but untested assumptions. These assumptions, which were tested over the ensuing decades, have enriched our understanding of metabolic regulation and the causes of diabetes. Currently accepted concepts emerging from modeling include: (a) the importance of sluggish insulin transport across the capillary endothelium in stimulation of glucose uptake; (b) the "single gateway" concept, that insulin transport across endothelium of adipose tissue suppresses free fatty acids, which act in turn to reduce endogenous glucose production by the liver; (c) the importance of the single gateway mechanism in the metabolic syndrome, whereby increased fat in the abdominal compartment relates to insulin resistance and risk for type 2 diabetes; and (d) the hyperbolic relationship between insulin action and insulin secretion, which provides an accurate prediction of diabetes risk. It is hoped that the experience with the metabolic system will provide a metaphor for other regulatory systems less subjected to critical quantitative analysis. Such analysis may well lead to analogous conceptual understanding of other important integrated biological systems, and provide approaches for early intervention in the pathogenic process of other chronic and devastating diseases.

Key Words: Modeling, minimal model, insulin resistance, β cell.

Personal Introductory Remarks

THIS MANUSCRIPT IS BASED ON the Irving L. Schwartz lecture, which I was honored to deliver at the Mount Sinai Medical School on November 9, 2000. In the preparation of such a lecture, it is customary to investigate the relationship between the lecture or lecturer, and the honored faculty member after whom the lecture was named. This provided a challenge to me. I was familiar with Dr. Schwartz' reputation, and his pioneering role in the Physiology Department at the Mount Sinai School of Medicine. But, as I assumed we were in different areas of research, and because I was never a trainee or faculty at Mount Sinai, it was unclear if I could make a meaningful personal comment regarding our possible relationship. This quandary led me to the latter-day oracle of all knowledge: the internet. I quickly struck cyber-gold. I noted that Dr. Schwartz had published, in 1965, an excellent review article in the *American Journal of Medicine* entitled "Insulin Structure and Function: Reflections on the Present State of the Problem" (1). Schwartz' co-author, Oscar Hechter, rang a large bell for me, as I also had published with him (2) (Fig. 1). More relevant: Oscar Hechter is my uncle! (See pedigree in Fig. 1). This unexpected co-author relationship between Dr. Schwartz and me was a very pleasant surprise; what was even more satisfying was that Irving Schwartz attended my lecture at Mount Sinai, and I think he also found the striking coincidence gratifying. I hope that the lecture and this manuscript will live up to the high standards set by Dr. Schwartz' work, as exemplified in the relevant article.

About Integrative Biology

There can be no denying the "molecular revolution" in life sciences over the past several

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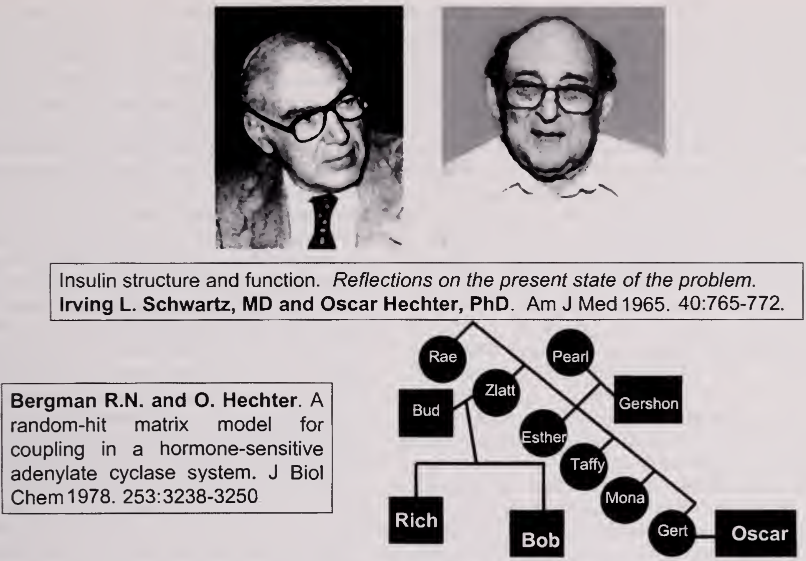
Adapted from the Irving L. Schwartz Lecture presented to the Department of Medicine at Mount Sinai School of Medicine, New York, NY on November 9, 2000 and updated as of January 10, 2002.



Insulin structure and function. *Reflections on the present state of the problem.*
Irving L. Schwartz, MD and Oscar Hechter, PhD. Am J Med 1965. 40:765-772.

Bergman R.N. and O. Hechter. A random-hit matrix model for coupling in a hormone-sensitive adenylate cyclase system. J Biol Chem 1978. 253:3238-3250

Fig. 1. Somewhat distant relationship between Dr. Irving Schwartz and the author. In 1965 Dr. Schwartz and Dr. Oscar Hechter published the cited manuscript in *American Journal of Medicine*. Bergman and Hechter published together in the *Journal of Biological Chemistry* in 1978. Pedigree diagram is that showing familial relationship between Hechter and Bergman.

decades. Molecular research has led to increasingly more accurate descriptions of the cellular events involved in hormone action. However, the elucidation of the human genome has generated a new and daunting challenge. How does one begin to integrate the mass of information which will emerge in an effort to comprehend biological function? It is clear that the integration of genomic information will profoundly change how life science research proceeds (3). It is also clear that mathematics and computer simulation will be a critical component of genomic studies. A senior investigator such as myself can only marvel at the coming challenges and insights which will emerge.

Ultimately, it will become necessary to integrate the mass of information which is emerging from the new areas of genomics and proteomics. Genome scans have revealed and will continue to reveal new molecules, which in turn will lead to the identification of new pathways. What will we want to know about these complex pathways? Certainly we must understand the "principles of regulation" which will reveal the "control points" that are most critical for alterations in metabolic function and for disease states. Much of the information will be redundant or unimportant. This has already become clear from transgenic studies; some knockout models are revealing information about human disease — others have led to investigation of models which are less than relevant. One might compare pugilists with scientists — In boxing the knockout is the end of the struggle; in physiology the "knockout" is only the beginning of the struggle!

A similar conundrum has existed in the molecular/systemic physiology relationship. This has been a difficult marriage indeed. It is difficult to avoid the siren song of reductionist research — one finding leads to questions regarding the underlying mechanism at a lower level of metabolic organization, with this pattern repeating so that information emerges at progressively greater and greater detail. One example is the insulin signaling pathway, which now is known to involve a surfeit of proteins that can account for multiple different potential signaling pathways. Will these studies reveal the causes of insulin resistance in type 2 diabetes? In this and other regulating systems, it is requisite to ask the question: "Will the principles of regulation of an integrated physiological system emerge from increasingly reductionist research?" It appears that the simple answer is probably not. We know this from the plethora of nonintuitive results which have emerged from knockout models. For example, knockout of the insulin receptor in skeletal muscle did not result in a murine model of diabetes (4). This outcome, which was a surprise to molecular biologists (5), was not surprising to those who had previously built models of carbohydrate regulation (6). The point is this: as with reductionist research, which marches in lock-step toward ever increasing detail, it is also necessary to study metabolic systems at higher levels of organization. Such studies may reveal principles of regulation which may never emerge from reductionist approaches.

The Role of Modeling — Studies from Our Laboratory

What is the paradigm for elucidating principles of regulation of an integrated physiological system? Endocrinology is an excellent playing field from which to study this question, as negative feedback regulation is part and parcel of regulation of hormones and metabolites. Fuel metabolism is of interest because it is essential to life, and because metabolic dysfunction — diabetes — is a major health problem in Westernized societies, accounting for more than 100 billion dollars in medical costs in the United States. But more important, diabetes is a major component of mortality, morbidity and human suffering in this country. Thus, for some years we have attempted to use concepts of systems analysis and modeling in parallel with experimental design to elucidate underlying principles of metabolic regulation in mammals. We hoped that by doing so we might impact the understanding of the mechanisms and the prevention of diabetes mellitus, and possibly advance therapy of the disease. If we have contributed meaningfully to these goals, we can believe that we have not been wasting our time or effort.

It Started with Minimal Modeling

The so-called "minimal model" has been widely published and widely used (7–9) (Fig. 2). It is interesting that the model was virtually uncited for the first 5 years after it was postulated and published — there are now approximately 50 major studies published per year employing the model, and more than 500 can be found in the literature. (This is a lesson to junior faculty — if you want to gain tenure don't veer too far from the established research paradigm!) Twenty years ago modeling had little impact on diabetes research, although a few models had been introduced (10–12). We considered that those models were either too simple or too complex, and hypothesized that a model of "optimal" complexity might exist — complex enough that the model could account for the feedback relationship between insulin and glucose, but simple enough so that it could be used to characterize metabolic function in a single patient with a simple clinical protocol. The history of the model has been written elsewhere (8, 13).

Over time, the minimal model has proven to be more than a clinical tool. The process of quantitative modeling forces explicit assumptions. Inherent in the model were some brazen assumptions unproven at the time the model was postulated. It is correct to say that a majority of the work that my colleagues and I have completed during the last 2 decades followed directly from efforts to test the simple assumptions inherent in the minimal model. The model made quantitative predictions, but the inherent concepts were qualitative in nature. In this article, I hope to relate some of the simple assumptions of the model to the work which emanated from testing these assumptions. While some of the work we have done has ventured far afield, the minimal model was always the basic road map. Of course the minimal model is far from perfect, but it has been an excellent vehicle to provoke some novel ideas and force experimental design.

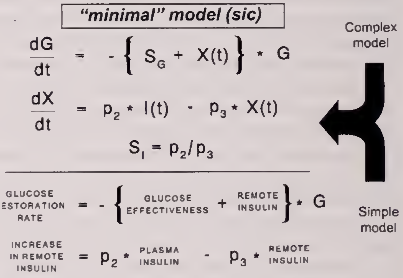

"minimal" model (sic)
$\frac{dG}{dt} = -\left\{ S_G + X(t) \right\} * G$
$\frac{dX}{dt} = p_2 * I(t) - p_3 * X(t)$
$S_I = p_2/p_3$
GLUCOSE RESTORATION RATE = - { GLUCOSE EFFECTIVENESS + REMOTE INSULIN } * G
INCREASE IN REMOTE INSULIN = p_2 * PLASMA INSULIN - p_3 * REMOTE INSULIN
Complex model
Simple model

Fig. 2. Equations of the minimal model. The minimal model was a compromise between complex and simplistic representations. The model accounts for the reattainment of basal glucose (G) and insulin (I) following glucose injection. Variable X is proportional to insulin in the remote compartment, now known to be interstitial insulin. Literal equations (top) are described in physiological terms below. First equation accounts for the post-injection decline of glucose in terms of insulin-independent as well as insulin-dependent processes. Second equation represents movement of insulin from plasma to interstitial fluid and internalization/degradation by insulin-sensitive tissues. Transport parameters represented by "p_x." S_I, insulin sensitivity index; S_G, glucose effectiveness. For details, see (6).

The Time Course of Insulin Action

Our modeling was based upon simple plasma kinetics of glucose and insulin. Surprisingly, in 1979, accurate dynamics of glucose and insulin after glucose injection had not been described, since infrequent sampling had failed to reveal the rich dynamic patterns that follow glucose injection. In the course of modeling frequently sampled data, we were absolutely unable to account for plasma glucose/insulin kinetics without a delay in the action of insulin to stimulate glucose utilization (7). Similarly, Rasio and colleagues described the slowness of insulin action in the dog (14, 15), and Andres and Sherwin and their colleagues implemented this idea in the 1970s in early glucose clamp studies (16, 17). Thus, there is a disconnect between the rapid action of insulin to mobilize glucose uptake *in vitro* versus its sluggish action *in vivo.* What is the explanation for the delay in insulin action to stimulate glucose uptake *in vivo*?

Clearly the difference between secreted insulin's action *in vivo* versus its action *in vitro* is the delivery of insulin to the insulin-sensitive tissues in the intact organism. Secreted insulin is distributed via the cardiovascular system to the capillaries of insulin-sensitive tissues (skeletal muscle, fat). The insulin molecule must then traverse the endothelium to gain access to the insulin-sensitive cells. It seemed reasonable that insulin's traversing of the endothelial barrier could account for its slow action *in vivo.*

How should transendothelial transport (TET) of insulin be examined? To study transport, it is necessary to access the compartment from which the peptide is coming and the compartment to which it is going. In the mid-1980s, George King and colleagues pioneered *in vitro* studies examining insulin transport across an endothelial cell monolayer, and suggested that transport was saturable and mediated via insulin-receptor binding on the luminal surface (18, 19). We reasoned that since sluggish insulin action is observed *in vivo,* we should study the transport process in intact animals. The compartments to be examined were blood (easily sampled) and interstitial fluid ("ISF"; difficult to sample *in vivo*) which bathes the insulin-sensitive cells. Following Rasio (14, 15), we used lymph as a surrogate for ISF.

Examining interstitial insulin (in dogs) revealed that even under fasting conditions there is a large insulin concentration gradient across the endothelial barrier (Fig. 3) (20). Under hyperinsulinemic conditions (as in glucose clamps) the gradient is maintained — even at pharmacological insulin levels (20, 21). Additionally, abrupt increases in plasma insulin provoke only sluggish increases in interstitial insulin, thereby accounting for our inability to model insulin action without a delay in insulin's effect. In contrast to plasma insulin, where the rapid changes were not mirrored by changes in glucose uptake, there was a near-perfect similarity in patterns of change in interstitial insulin compared to glucose utilization (Fig. 3). These data confirm that transendothelial transport of insulin is the primary process which limits the rapidity of changes in glucose disposal in response to changes of insulin in blood.

Thus, modeling led to the understanding that TET is one of the most important factors determining insulin action dynamics. TET insulin delivery is also a critical factor in the efficacy of insulin-like analog molecules (22). The question arises as to whether TET is altered in pathological states. Recently, Hamilton-Wessler and Ellmerer, in our laboratory, have demonstrated that TET may be reduced in a model of insulin-resistant central adiposity (23) (Fig. 4). While these studies require confirmation, it is possible that TET may be a cause of insulin resistance under some conditions, and thus may be an important target for therapy.

The Liver

Normally, insulin response not only stimulates glucose utilization, but squelches endogenous glucose production (EGP) from the liver. If TET is rate limiting for activating glucose uptake, what determines the kinetics of suppression of EGP? Liver capillaries are fenestrated — therefore, following the secretion of insulin into the portal vein, the peptide should reach the liver almost immediately and suppress EGP. It is true that insulin can be detected rapidly at the liver following hormone injection (24) (Fig. 5). Yet, despite rapid accumulation of hormone in liver, EGP is suppressed slowly (25) (Fig. 5). How can the paradox of insulin's rapid accession of hepatocytes, yet relatively sluggish suppression of EGP, be explained?

The discordance between portal insulin concentration and suppression of glucose production led us to hypothesize that there is an intervening signal mediating insulin's action to reduce EGP. We hypothesized that insulin acts first at some "initial recognition" tissue depot with a relatively impermeable endothelial barrier (i.e., not the liver). Following this initial recognition there would be modulation of a sec-

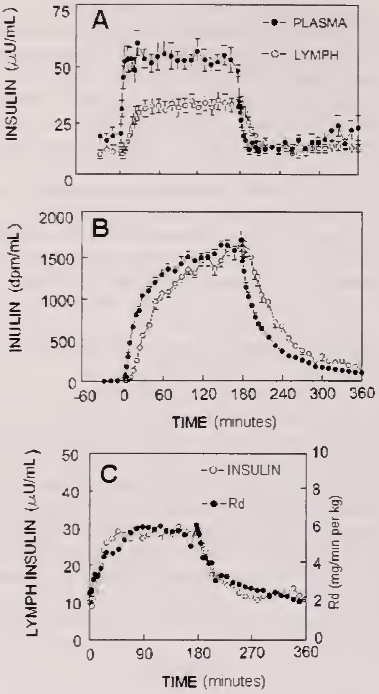


Fig. 3. Results from euglycemic glucose clamps. Insulin (**A**) and inulin (**B**) were infused intravenously under euglycemic conditions. Samples were collected in plasma as well as lymph (surrogate for interstitial fluid). Insulin levels in interstitium were lower than in plasma ("attenuation") at basal and during activation period of clamps. Insulin rises rapidly in plasma, but slowly in interstitium, reflecting delay in transendothelial insulin transport. Unlike insulin, there is no steady-state plasma:interstitium gradient for inulin due to lack of cellular uptake of the inert compound. **C.** Hand-in-glove similarity between interstitial insulin and glucose uptake (Rd). Adapted from (20).

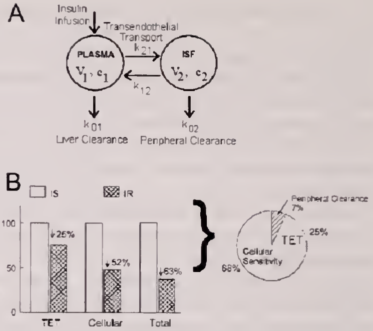


Fig. 4. Role of transendothelial transport (TET) defect in insulin resistance of obesity. **A.** Compartment model representing flux between plasma and interstitial fluid (ISF). "k" parameters are fractional transport coefficients. "V" are volumes of distribution for insulin, and "c" are concentrations. **B.** Bar graph shows estimated contribution of TET defect compared to defect in insulin-sensitive cells to overall insulin sensitivity. IS = insulin-sensitive group; IR = insulin-resistant group.

ondary signal, which then itself controls glucose output. We considered several recognition tissues and secondary candidates (Fig. 6). One favored candidate emerged: under a variety of conditions, a remarkable correlation was observed between plasma free fatty acids (FFA) and glucose production rates (22, 26–29) (Fig. 7). FFA in blood under fasting conditions emanates from triglycerides stored in adipose tissue depots. Because adipocytes have an impermeable endothelial barrier similar to skeletal muscle, the sluggish effect of insulin could be explained by slow permeation into adipocytes, slow suppression of lipolysis, reduction in plasma FFA, and ultimately reduction in EGP ("single gateway hypothesis") (25, 30, 31) (Fig. 8). Thus, plasma FFA has emerged as a potentially important regulator of glucose production, which can be modulated by insulin.

Importance of FFA Control of Endogenous Glucose Production

The scientific journey leading to postulation of FFA as an important moment-to-moment controller of liver glucose output was founded in our inability to account for effects of insulin on glucose uptake and production without postulating a delay in the effect of the hormone. Thus, it was an indirect outcome of the need to postulate the delay in insulin action on EGP in the minimal model. However, the concept of FFA regulation of glucose production has important implications for the pathogenesis of type 2 diabetes.

Population studies have revealed a striking relationship between central, or visceral, adiposity and the risk for both type 2 diabetes and cardiovascular disease (32, 33). While obesity is generally associated with insulin resistance (34), the correlation between central adiposity and resistance is even stronger (35). We considered the possibility that there is a causal relationship between visceral fat and insulin resistance, and that this relationship is due to the role of FFA in controlling liver glucose output.

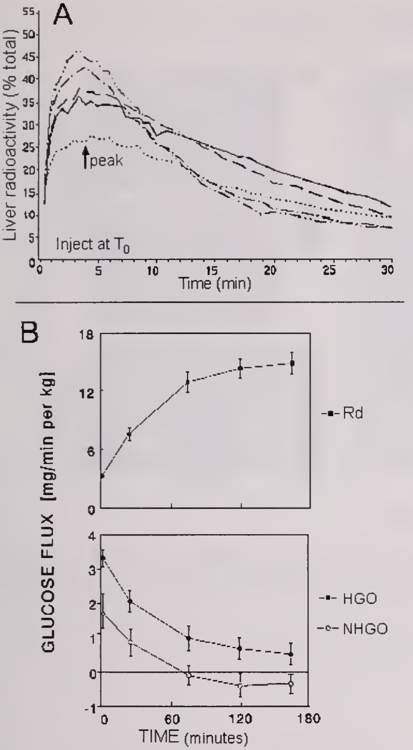


Fig. 5. A. Rapid distribution of injected radioactively labeled insulin in liver (modified from Jensen et al.) (24). **B** (top). Comparatively sluggish increase in glucose uptake (Rd) and equivalently slow suppression of glucose production (bottom) in dogs during euglycemic clamps. HGO and NHGO = hepatic and net hepatic glucose output, respectively. Insulin administered at 20 pmol/min per kg. From (25).

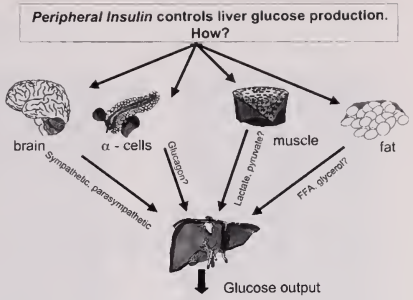


Fig. 6. Possible signals by which peripheral insulin may regulate endogenous glucose production. FFA = free fatty acids.

To examine the role of central lipid accumulation we introduced a model of visceral adiposity in the dog (36). We increased the fat content of the diet by 2 g/kg per day, which is a modest amount, especially when compared with diets used by other laboratories (37, 38). This modest increment in fat intake produced a canine model of the "insulin resistance syndrome" (Fig. 9). To establish the causality of changes in metabolic function induced by dietary fat, we used the minimal model to measure insulin sensitivity at 2-week intervals for 12 weeks of fat feeding. The pattern of changes was interesting and unanticipated. As expected, with fat feeding, insulin sensitivity declined within 1 week to a level of 40% of normal. Unexpectedly, insulin secretory compensation to the insulin resistance was not observed until the second week. First-phase insulin release maximized at week 6, but then receded, reaching a value slightly higher than basal by the 12th week. Despite this pattern of changes, there was little change in glucose tolerance. The question arises: how was insulinemic compensation for insulin resistance maintained despite only a transient increase in secretion by the β-cells?

Interestingly, after 6 weeks of increased fat in the diet, the need for increased insulin secretion was mitigated by a very substantial reduction in metabolic clearance rate of the hormone. Most insulin is cleared by the liver. Fat feeding induces a reduction in first-pass hepatic clearance of insulin, mirrored by a reduction in the number of insulin receptors (39). The reduction in receptor-mediated insulin clearance is a very important component of the integrated metabolic response to compensate for insulin resistance. Thus, the liver acts as a "gate-keeper," titrating the proportion of newly secreted insulin reaching the systemic circulation and insulin-sensitive tissues (muscle and fat). This physiological role of the liver can be viewed teleologically — it can explain why evolution has provided that insulin is secreted into the portal vein — with the liver modulating release of newly secreted insulin into the systemic vessels. It is clear that normal function of this gate-keeping function can relieve the β-cells of hypersecretion of insulin. Is it possible that failure of the liver to regulate insulin clearance in proportion to physiological need may stress the β-cells and contribute to the pathogenesis of Type 2 diabetes?

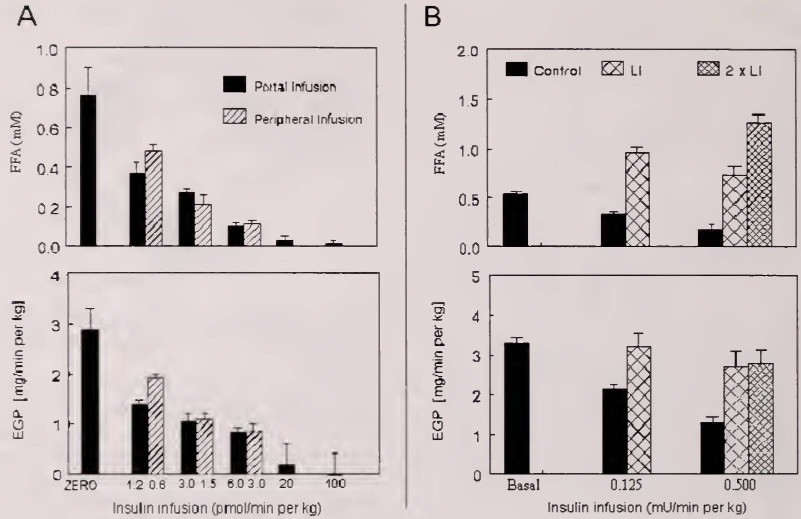


Fig. 7. Data supporting free fatty acids (FFA) as the peripheral signal regulating liver glucose production. **A.** Insulin was infused in conscious dogs either into the portal vein (black bars) or into a peripheral vein (striped bars) at rates selected to yield similar peripheral insulin levels. Infusion rates were approximately doubled for portal infusion to compensate for first-pass hepatic clearance of insulin. Note the striking similarity in pattern between effects of insulin on plasma FFA (top) compared with endogenous glucose production (EGP, bottom). From (26). **B.** Infusion of Liposyn with heparin (LI) (hatched bars) prevented the fall in FFA as well as the decline in glucose production, further supporting FFA role as signal to the liver. From (27). [**Editor's Note:** LI = 20% safflower oil emulsion administered at 0.5 mL/min, 2 × LI = the same solution administered at 1.0 mL/min.]

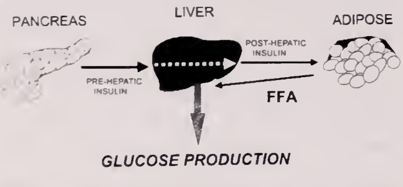


Fig. 8. The "single gateway hypothesis." Insulin is envisioned as controlling glucose output indirectly. The hormone is secreted by the β-cells of the pancreas, from which it enters the liver. While insulin may have a direct acute effect to suppress EGP, much of it survives first-pass degradation and enters the systemic circulation where lipolysis is suppressed in adipocytes. Reduction of plasma FFA is a major factor lowering liver glucose production. Because adipocyte endothelium is relatively impermeable to insulin, this mechanism can explain the surprisingly slow effect of any increase in insulin to suppress EGP. For details, see (30).

Thus, visceral adiposity contributes to increased flux of FFA to liver, reducing insulin clearance and potentially stimulating glucose production. In fact, both Joyce Richey and Stella Kim have recently demonstrated, in the rat and the dog, respectively, that after chronically increased fat intake, glucose production by the liver is rendered totally resistant to insulin, such that a physiological increase in the portal level of the hormone fails completely to suppress steady-state glucose output (40, 41). The insulin resistance explained by increased portal fatty acid flux is exacerbated by the extreme insulin resistance of the visceral adipocytes, shown *in vitro* (42) and recently confirmed *in vivo* (43). Thus, portal FFA flux to the liver can account for the relationship between visceral adiposity and insulin resistance. Other molecules emanating from adipocytes may also bear responsibility for insulin resistance, including cytokines such as tumor necrosis factor (TNF)-α or interleukin-6. Newly described peptides such as resistin (44) or adiponectin (45) may also play a role. However, we continue to support the concept that it is the enhanced turnover of visceral FFA, resulting in fat accumulation in the liver, which plays the primary role.

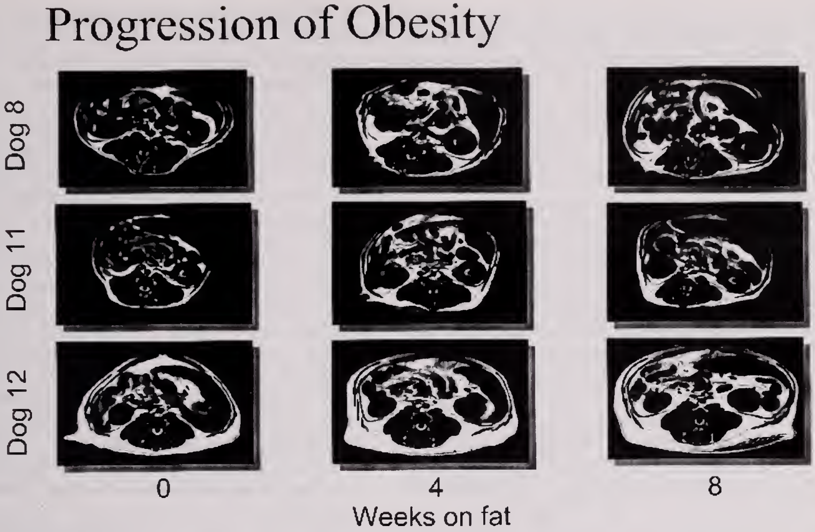


Fig. 9. Progression of central obesity in the dog with a modest fat diet. Diet was increased by 2 g/kg per day of fat. Note increase in visceral as well as subcutaneous fat (white area) from magnetic resonance images (MRI) collected before diet and at 4 and 8 weeks.

Our studies of the importance of central fat are an indirect result of trying to explain why suppression of glucose production of liver in response to hyperinsulinemia occurs slowly — a necessary assumption of the minimal model!

The Hyperbolic Law of Glucose Tolerance

Great battles die hard. In the glucose regulation area, one of the primary battlefields has been the relative importance of insulin resistance versus pancreatic β-cell dysfunction in the pathogenesis of type 2 diabetes (46–48). The surprising hyperinsulinemia of obese patients following glucose ingestion, first identified in New York by Berson and Yalow (49), was suggestive of insulin resistance — elevated insulin with reduced glucose tolerance. Perley and Kipnis, however, demonstrated that when the blood glucose signal was carefully matched, noninsulin-dependent diabetic patients had reduced plasma insulin values (50). The introduction of accurate methods for measuring insulin sensitivity, including the minimal model (6, 51) as well as β-cell response (52–54), did not resolve the controversy over the importance of insulin resistance versus β-cell dysfunction.

We believe that dynamic modeling contributed to the present truce (resolution) regarding the resistance/dysfunction controversy. The resolution emerged from a well-accepted engineering concept known as the “closed loop gain,” which is calculated from a closed-loop negative feedback system (such as the glucose regulating system) and reflects the contribution of all compensatory elements to the ability of the system to regulate itself. With respect to glucose regulation, while many factors can contribute to glucose disposal, insulin secretion and insulin action are the primary elements which determine the ability of the intact organism to respond to provision of fuel. Clearly, insulin resistance can be compensated by enhanced secretion, and a secretory defect will be less significant when there is robust insulin sensitivity. We therefore defined the “disposition index (DI)” as the product of insulin response and insulin sensitivity. Because insulin resistance is compensated in healthy individuals by an increase in β-cell responsiveness (36, 55, 56), DI can be interpreted as the responsivity of the β-cell normalized to the degree of insulin resistance.

The DI can best be appreciated by plotting the relationship, for a group of individuals, between secretory response and insulin sensitivity (Fig. 10). Because we envision the β-cells compensating for insulin resistance (rather than the reverse), we plot sensitivity as the independent variable and β-cell function as the dependent variable. The hyperbola (Fig. 10) represented by:

Insulin sensitivity* × *Insulin Secretion = DI

(or the "DI-perbola"), encompasses the idea that reduction in insulin sensitivity due to environmental factors (e.g., infection, obesity, pregnancy, puberty, aging) will be compensated by a proportional increase in β-cell response. In a given individual, the ability of the β-cells to upregulate sensitivity to glucose in response to a decrement in insulin sensitivity is quantitated by the DI value for that individual. A population DI can also be calculated (57). What then characterizes disease?

Risk for diabetes can be characterized as a reduced ability of the β-cells to compensate, i.e., a reduced DI. We hypothesize that the DI value for subjects at risk for diabetes will be lower than normal — even under insulin-sensitive conditions. We may therefore be able to identify subjects at risk for type 2 diabetes long before onset of the disorder by measuring insulin sensitivity and β-cell response, calculating the product, and comparing the result with a similar product from a "normal" (i.e., not at-risk) population.

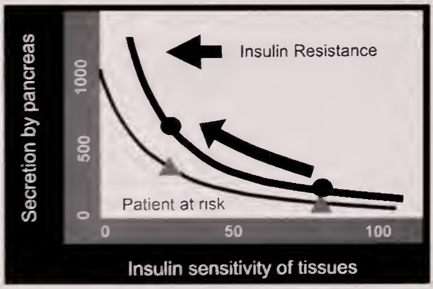


Fig. 10. The "DI-perbola," the classical hyperbolic relationship between insulin secretion and insulin sensitivity. In normal individuals (thick hyperbola, black dots) arrow indicates shift from insulin-sensitive to insulin-resistant state. With insulin resistance, increased β-cell sensitivity will compensate, thus maintaining glucose tolerance in the normal range. In subjects at risk for diabetes, a similar shift to insulin resistance (thinner hyperbola, triangles) should cause a lesser increase in secretory function, signaling a subtle β-cell defect. The equation of either hyperbola is Secretion × Sensitivity = Disposition Index ("DI"); the value of the DI is lower for an at-risk individual.

DI also emanated conceptually from the minimal model. We were able to calculate a parameter of insulin sensitivity by fitting the model to intravenous glucose/insulin dynamics. This insulin sensitivity index, S_I, has been widely regarded as a quasi-universal measure of insulin action (58). S_I measures the ability of a given increment in plasma insulin to enhance net glucose clearance. The mean value in a normal population is approximately 5×10^{-4}/min per μU/mL.

DI has been a useful concept. Bogardus, Pratley and colleagues have demonstrated that the risk for type 2 diabetes in the Pima Native Americans is about 20 times greater for the lowest 10% compared to the highest 10% of values of DI (56). Elbein, Kahn and colleagues have demonstrated that DI is heritable (59). Thus, DI, a concept which emerged from minimal modeling considerations, is presently one of the most useful parameters for expressing future risk of type 2 diabetes. Given the difficulty in finding one, or even several, major risk factor genes for type 2 diabetes, it is probable that DI which emerges from a clinical test may well be our most potent weapon for predicting type 2 diabetes in the near future.

Final Comments

Quantification is a final and crucial step to the history of any scientific endeavor. The importance of quantification is not questioned in physical science — we are in awe of the revolutionary transition from the "qualitative" science of Archimedes to the quantitative physics of Newton and Einstein. Conceptualization and quantification of entropy were fundamental to chemistry as well as to information theory. It is less appreciated that quantification may well lead to a similar revolution in biological science. In many ways biological science is just now entering its quantitative era. This is abundantly clear in molecular genetics, which is a close relative of information sciences. In genetics, measurements which are critical to a quantitatively based theory are easily made. However, it is difficult to measure the plethora of protein signals emerging from the genome. It will be even more difficult to integrate the mountains of data which will emerge when the relationships between the genome and the families of proteins can be exploited.

The purpose of this article is to point out that emergent principles can be elucidated from complex systems at any level of integration. We were fortunate to benefit from concepts in systems engineering as well as from biology, to try to comprehend some of the underlying principles which maintain the supply of fuel to higher organisms. The process of modeling and quantification forced us to define in quantitative terms the most important state variables in glucose regulation, including insulin sensitivity, first-pass hepatic insulin clearance and β-cell responsiveness. In the process of examining the relationship among these variables certain important relationships were realized, including insulin's slow effect, temporal changes in insulin clearance, and the hyperbolic relationship between insulin action and insulin secretion. It is of interest, for example, that sluggish insulin action ultimately led to the importance of FFA in the "metabolic syndrome" (Fig. 11). For us it has been a long, somewhat tortuous, but exciting conceptual journey. I can only hope that I can add to the outstanding contributions of Dr. Irving Schwartz, and that our journey might provide a template for a more junior population who will have to deal with the really hard problems.

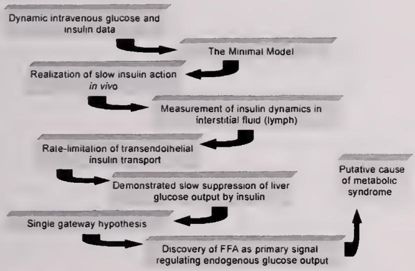

Dynamic intravenous glucose and insulin data
The Minimal Model
Realization of slow insulin action *in vivo*
Measurement of insulin dynamics in interstitial fluid (lymph)
Rate-limitation of transendothelial insulin transport
Demonstrated slow suppression of liver glucose output by insulin
Putative cause of metabolic syndrome
Single gateway hypothesis
Discovery of FFA as primary signal regulating endogenous glucose output

Fig. 11. Historical progression of research in our laboratory. The minimal model was based upon frequent measurements of glucose and insulin in plasma following glucose injection. Slowness of insulin action was a necessary postulate in the model; this led to realization of slow transendothelial transport of insulin, as reflected in sluggish changes in interstitial insulin concentrations. Similar slow dynamics of insulin action on liver glucose output and glucose uptake revealed extrahepatic site of insulin action and indirect effect of insulin to suppress glucose output. Realization that FFA were a signal controlling liver glucose output may explain the negative effect of central adiposity on insulin sensitivity, and risk for diabetes and other chronic diseases (metabolic syndrome).

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The Small World of Global Health

Jeffrey P. Koplan, M.D., M.P.H.

Abstract

This article is based on the Solomon Berson lecture, delivered by Dr. Koplan in January 2000. In his remarks, Dr. Koplan discussed the current status of global health and projected trends in three categories: communicable diseases, risk factors for disease, and selected diseases and health conditions. Reflecting on differences in health issues in the 30 years since he left Mount Sinai, Dr. Koplan pointed out that the health problems of developed and developing nations are strikingly similar now — which also means they are amenable to similar interventions.

Key Words: Global health, developing nations, communicable diseases.

Introduction

In the 30 years since I left Mount Sinai, there has been a true sea change in the homogenization of health issues around the world. In 1970, the health problems of the West and developed nations were chronic diseases. For less developed countries, the health problems were infectious diseases, coupled with a great concern about population growth.

In contrast, today, the spectrum of health issues is largely the same for most nations, and the relative contributions of chronic and infectious diseases will only become more alike over time. Increasingly, regardless of whether we live in an industrialized country or a developing one, the health problems we face are strikingly similar — and will only become more so if current trends continue.

In this article, which is based on a lecture I was honored to give at the Mount Sinai School of Medicine in January 2000, I would like to discuss our current global health status and projected trends in three categories:

1. communicable diseases
2. risk factors for disease
3. the diseases and health conditions themselves.

Transitions

A number of factors have contributed to the homogenization of organisms, exposures, risk factors, and vectors. These include:

- the increasing volume of travel, which has led to quantitative and qualitative differences in the number and types of people from different places moving around the globe, for short-term travel as well as more extensive and permanent migration

- a global marketplace that creates a demand for the free and constant movement of produce and other goods around the world.

Another way to think about this shift from the diseases of poverty (maternal and childhood illnesses and infectious diseases) to the diseases of affluence (such as ischemic heart disease, cancer, diabetes, and injuries) is in terms of epidemiologic, demographic, and behavioral transitions.

The epidemiologic transition occurs as countries become more industrialized and their populations become more affluent and educated. These technological and social changes

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influence the types of risk factors to which populations are exposed, typically shifting the major causes of death and disease from infectious diseases (gastroenteric and respiratory infections) to chronic, degenerative diseases.

It is worth noting that although many developing countries move steadily from a health profile dominated by infectious diseases to one dominated by chronic diseases, reverses are also possible. Parts of the former Soviet Union have experienced terrible setbacks as their public health infrastructures have crumbled and their populations have succumbed to a wide variety of preventable diseases.

Demographic transitions in countries or regions occur when fertility and birth rates decline at the same time that health improvements lead to increases in the number and proportion of elderly people. Migration patterns also affect the pace and scope of demographic transitions — not just among nations, but from rural to urban areas.

As both developed and developing countries have gained control over infectious diseases, the risk factors associated with the luxuries of non-subsistence living — tobacco, alcohol, increased dietary fat, inactivity, cars, and pollution — have loomed larger. These risk factors are the basis for the third type of transition: a behavioral transition. And unlike their microbial counterparts, these risk factors emanate largely from our own economic and cultural habits — habits that we are increasingly exporting to the rest of the world through marketing, entertainment, and economic clout.

These adverse side effects of economic progress and development counterbalance in disease burden the considerable progress we have made against infectious diseases. Most important, they are risk factors that we — as individuals, as communities, as governments — can influence to a far greater degree than we have demonstrated so far.

Communicable Diseases

Of course, no nation can ever completely transition away from infectious diseases, even if their relative burden decreases. At Mount Sinai's medical center, health care professionals daily confront hospital infections, antibiotic resistance, influenza, TB, HIV/AIDS, and so on. Infectious diseases have always been mobile and moved into new, susceptible populations. Among the many examples are the introduction of yellow fever from Africa into the Caribbean and South America; the introduction of measles and smallpox into the Western hemisphere; and the worldwide circulation of influenza.

The ease and practically instantaneous speed of current transportation methods have helped microbes move freely around the globe, along with the rest of us. Jets not only transport many people quickly to every corner of the earth, but they increasingly move people to and from formerly remote places. Tourism is part of this picture, but so are the vast migrations that follow in the wake of wars, economic disruption, and the subsequent searches for safety and economic opportunity.

Beyond airplanes, global shipping of foods and other products, while slower and less dramatic than jet travel, is a major transporter of disease vectors. Even in our own backyards, suburban encroachment of wild habitats puts more and more of us into the path of the deer ticks that cause Lyme disease, rabies carried by racoons, or even the dung-infested dust particles that carry Hantavirus from rodents to humans.

A case two years ago in Tennessee teaches us the same lesson as the West Nile encephalitis outbreak that first surfaced in New York: just because it has not been seen in this hemisphere, or in humans, does not mean we can rule it out.

In the Tennessee case, a channel-surfing nurse happened to watch a television show about vector-borne diseases, which featured footage of the reduviid or "kissing bug" — an insect that transmits *Trypanosoma cruzi*, the parasite that causes Chagas' disease in humans. After watching the TV show, the nurse went into another room to check on her 4-month-old baby, and there in the crib she saw the exact same bug she had seen on TV. Amazingly, she preserved it and sent it to a university lab for analysis, from which it was forwarded to us. The bug was indeed exactly what she thought it was. It carried the parasite *Trypanosoma cruzi*, and the baby had been infected.

We at Centers for Disease Control and Prevention (CDC) investigated this case and could find no other reduviid bugs in any of the houses near hers, nor could we find any other evidence of human infection. We had to conclude that this isolated event was probably the result of the bug hitchhiking, undetected, in a South or Central American migrant worker's belongings. Like Hantavirus and West Nile encephalitis, this was a transmission we had not seen before in the United States. And like those diseases and vectors, we know that if we start looking, we will find more.

Each year, CDC investigates hundreds of outbreaks like these, 90% of which involve infectious agents. We know these are just the tip of the iceberg — the ones that are serious enough, or intriguing enough to someone, to get on our radar. We know that the mobility of people in the world and in this country is unprecedented in human history, with fewer financial and social constraints than ever before.

Both close to home (such as recent malaria cases traced to Long Island, Dengue fever in Texas) and far afield (such as nipavirus outbreaks among pigs in Malaysia; Ebola and Marburg in central Africa; new avian influenza strains in Hong Kong; and of course the looming threat of pandemic flu), we at CDC want to be vigilant about emerging infectious diseases. But, as the examples of Chagas, West Nile, influenza, and TB illustrate, we have a broad and varied range of threats to monitor - new vectors in unexpected places, old vectors appearing in new hosts, and everything from travelers to immigrants to fresh produce helping them along. And even more recently, we have had the horrific experience of investigating cases of anthrax, unleashed by one or more bioterrorists.

In the past 30 years, 30 new infectious agents have been identified around the world. Again, we know that the harder we look, the more we will find, and we will likely have dozens more in the years to come. Whether they emerge as a result of natural mutations or because of a manmade bioterrorist event like the recent anthrax cases, we take our preparation against these bugs very seriously.

From these examples, one should not conclude that developing countries exclusively pose the threat of communicable diseases, against which those of us in the West must guard ourselves. For example, in many countries (including China), HIV/AIDS is viewed as a Western import, spread by promiscuous and immoral travelers.

In fact, risk factors and diseases move along a two-way street. Just as travel brings us into closer contact with new microorganisms to which we would never have been exposed before, a number of forces — communication, entertainment, the growth of market economies — expose people in other parts of the world to many aspects of our lifestyle. Some of these are detrimental to health and serve as risk factors for serious diseases and health conditions.

Risk Factors: Global Convergence in Tobacco Use, High-Fat Diets, and Motor Vehicle Crashes

Today, chronic diseases account for less than half of the deaths in developing countries, but by 2020, if current trends continue, this proportion will increase to 7 out of 10 deaths (1). In 1990, chronic diseases superseded infectious and parasitic diseases as the cause of death in every region of the world except sub-Saharan Africa. Yet even in sub-Saharan Africa, chronic disease rates are ascending, and infectious and parasitic diseases are declining — a testament to successful immunization campaigns and other types of interventions. There is no question, though, that by the time data from the end of the 1990s are available, chronic diseases will have surpassed infectious diseases as the leading cause of death around the world. Globally, this means that both risk factors and causes of death are converging.

When we examine the threats to health that we can prevent, many are rooted in chronic diseases and injuries. The global impact of several of these — particularly tobacco use, diet, and motor vehicle crashes — is compelling. More important, these are risk factors that we can actually do something about. The combination of individual behaviors and health promotion policies that influence these risk factors may seem mundane, compared to the more exotic infectious diseases. But their impact is real and growing.

Tobacco

Worldwide, tobacco accounted for 4 million deaths in 1998. By 2030, this figure will rise to 10 million — more than the total deaths from malaria, maternal and major childhood conditions, and TB, combined. Half of these deaths will occur in the 35–69 age group, with an average loss of 20–25 years of productive life. Seventy percent of these deaths will occur in the developing world (2).

Thanks to vigorous tobacco control efforts here and in other high-income countries, tobacco consumption has generally fallen in the developed world since its peak years of the mid-1960s, when 40% of Americans smoked (and 60% of American males, including our Surgeon General).

But smoking prevalence is increasing in developing countries, at a rate of 3.4% per year. In contrast to our current rate of 23%, smoking prevalence among men in developing countries is approximately 48%. Of the 1.15 billion smokers in the world today, 82% live in low- and middle-income countries (3).

Consider this: the largest tobacco company in the world is not Philip Morris or RJ Reynolds, but the China National Tobacco Corporation, which produced nearly a quarter of the world's cigarettes in 1997 (4). In China, 70% of adult men smoke (5). Unlike their Western counterparts, many Chinese lack even basic information about the hazards of smoking. A 1996 survey of Chinese adults revealed that half of smokers — and half of nonsmokers as well — believed that there was little harm in smoking. Only 4% of the survey respondents could correctly identify a connection between smoking and heart disease (6).

What is behind these consistently high smoking rates? Profits. The world retail market in cigarettes is estimated to be worth $300 billion. Tobacco companies are hugely profitable, and as consumption falls in high-income countries, the developing world has become an ideal market for expansion. Developing countries are tantalizing to tobacco companies because they offer a package of untapped markets combined with few or nonexistent restrictions on advertising.

There is one small exception to the flow of tobacco exports from the United States to developing countries, and that is the growing popularity of *bidis* — hand-rolled, flavored cigarettes from India — among teenagers here in the United States. A survey of Massachusetts teenagers in 1999 indicated that 40% had smoked bidis at least once, and 16% were current smokers (7). Most disturbingly, many of the teens believed that bidis are safer than cigarettes. Nothing could be further from the truth. Their cherry, chocolate, and mango flavoring masks the fact that they produce about three times the amount of carbon monoxide and nicotine and nearly five times the amount of tar as cigarettes — and bidi smokers inhale more often and more deeply because of the characteristics of the cigarette's leaf wrapper.

In any case, in the developing countries where tobacco consumption has not increased, there is the potential to avert the massive health care costs and tobacco-related morbidity and mortality that we know all too well here in the United States, and that faces China and many other countries if current consumption patterns persist.

Diet and Nutrition

In developing countries, the overwhelming dietary problem is often under-nutrition. But as nations and their residents become more prosperous, a paradoxical set of new hazards appears, brought on by higher consumption of meats, fats, processed foods, and total calories.

In China, one of the most rapidly industrializing nations in the world, fat intake has increased rapidly, especially among the higher-income populations that are concentrated in urban areas.

At its most extreme, over-consumption of foods can be seen in levels of obesity among adults and, sadly but with increasing frequency, among children.

In this country, we are experiencing an epidemic of obesity.

Diet and nutrition are areas where our health habits constitute a dangerous export to the rest of the world. For years, we have been intrigued (and made green with envy) by the "French paradox" — the seeming ability of the French to eat foods rich in artery-clogging saturated animal fat, yet avoid mid-life heart attacks. Several possible explanations for this phenomenon have been offered over the years, including the protective role of wine, moderate drinking, fiber consumption, and portion sizes — among others.

Whatever the explanation, the French seem to be losing their protection against the adverse effects of fat consumption. The consensus seems to be that French fat consumption has increased steadily over the last 20 years, and that heart disease rates — with their typical delayed manifestation — will catch up. But the increased fat consumption is not from richer sauces, fabulous pastries, and extra helpings of foie gras. Instead, the French have consumed more fat because their diets have become more Americanized (8).

The French now eat more meat and fast foods, snack more, eat fewer regular relaxed meals, exercise less, and drink less wine than they used to. But while they may be getting heavier, their obesity rates still lag far behind ours: 8 percent of French adults, versus 30 percent of American adults.

Motor Vehicles and Collisions

In developing countries, the escalating rates of motor-vehicle-related death and disability provide one of the best examples of the unintended negative consequences of economic development, as motor vehicle deaths and injuries keep pace with increasing numbers of cars on the roads.

Those who have traveled in developing countries can readily understand why deaths and severe injuries are more commonplace. On poorly maintained roads with *laissez faire* enforcement of traffic laws, cars jostle with overcrowded buses, motorcycles, mopeds, rickshaws, bicycles, and pedestrians. In developing countries, half of all motor vehicle fatalities are among pedestrians and drivers of two-wheeled vehicles. Mortality rates per vehicle in Ethiopia and Nigeria are 50 times higher than in the United States and the United Kingdom (9).

This helps explain recent data from an internal Peace Corps analysis of deaths among Peace Corps volunteers. Although Peace Corps volunteers end up in some rather remote places, where one might expect them to be exposed to exotic infectious diseases, the leading cause of death by far is unintentional injuries, to which motor vehicle crashes are the largest contributor.

Injury prevention and control is an example of a health problem grown common in all parts of the world, with solutions and interventions that are largely applicable in all parts — from seat belts, air bags, child safety seats, better car and highway design, regulations and their enforcement, de-linking alcohol and driving, driver education, and many other interventions.

Similarly, models of risk factor reduction for chronic diseases such as coronary heart disease can be used worldwide. We in the United States have learned and applied a lot from the experience of our Finnish colleagues.

North Karelia, Finland, provides perhaps the best example of how a combination of individual health education and strong, across-the-board changes in policies achieved dramatic results.

Although our stereotype of Finns is of healthy, lean cross-country skiers subsisting on pickled herring and dark bread, in reality, at least in the early 1970s, they had very high rates of smoking and truly astounding patterns of animal fat consumption. These, in turn, had led to excessive heart disease mortality rates among the Finns, both men and women.

Over a 20-year period, the Finns implemented a “full-court press” on heart disease. In addition to physician education and media campaigns about cholesterol, blood pressure, and smoking, the dairy industry was persuaded to provide low-fat versions of milk and cheese. Between 1972 and 1992, heart disease deaths among men declined 68%, and among women 55%. Perhaps most encouraging was the fact that these lifestyle changes seeped into Kuopio, the control region next to North Karelia, until both regions achieved similar reductions by the end of the second decade (10).

This tells us that when we persuade people that these changes can be made, and when policies support those changes, large-scale adoption of healthy behaviors can occur. So we know that a combination of individual health education and broad policies to promote health is critical — one without the other will not get us very far. And we know that it takes a long time — decades, in fact — to create these kinds of changes. Dramatic reductions in tobacco use in this country over the past 30 years are yet another example.

The same is true for motor vehicle injuries. In countries where motor-vehicle fatalities and injuries have declined — like ours — we have demonstrated that separating traffic of different modes and speeds, training drivers, enforcing seat belt and drunk driving laws are effective policies. Many of these interventions also were pioneered in other countries — yet another reminder that we have much to learn and adapt from the rest of the world when it comes to health and safety.

Changing Disease Patterns and Burdens

Tobacco use and dietary habits are risk factors for various chronic diseases and states of ill health, such as coronary heart disease, diabetes, and hypertension; while motor vehicles clearly take a toll not only in terms of injuries and fatalities, but also by reducing physical activity and increasing pollution.

I would like to discuss these trends more broadly by examining changing disease patterns and burdens around the world.

DALYs: Documenting the Burden of Disease

As noted earlier, chronic diseases and injuries have overtaken communicable diseases as the leading causes of death in much of the world, and this trend is likely to accelerate. But mortality is only one way to measure health trends. Disability-Adjusted Life Years, or DALYs, give us another portrait of the same trend.

DALYs combine measures of disease incidence, prevalence, severity, and mortality into a single measure. We have used this technique to examine the 10 leading causes of DALYs in the United States.

DALYs have drawn some criticism recently on several fronts, questioning their usefulness for monitoring and comparing population health across countries and identifying priorities for interventions, research, and development (11). Although any measure as complex as DALYs offers room for improvement (as its original architects would be the first to agree), there is no question that DALYs have greatly informed debates about the health status of populations and how to improve them. As just one example, a major benefit of using DALYs rather than mortality alone is that it allows us to account for the burden caused by conditions that produce considerable disability — such as arthritis or depression — but that are not associated with high mortality rates.

The 10 leading causes of DALYs in the United States in 1996 are shown in the Table (12). One item not on the list — HIV — is something other than a chronic disease, a mental illness, or a type of injury. (And certainly an argument can be made that HIV shares many features with chronic diseases, irrespective of its infectious origins.)

DALYs are another way of looking at the epidemiologic transition described earlier. As both developed and developing countries have gained control over infectious diseases, the risk factors associated with the luxuries of non-subsistence living — tobacco, alcohol, increased dietary fat, inactivity, cars, and pollution — have loomed larger. Whether we use DALYs, mortality, or other measures, we are likely to see a convergence of risk factors and causes of death not only in the industrialized world, but between the developed and developing worlds as well.

Although comparisons between different countries and regions are instructive, we must also remember that nations are not necessarily homogenous in terms of health status. Just as the poorest countries have subgroups who enjoy better health and longevity than their fellow citizens, so too do richer countries harbor pockets of extreme poverty and disease. Unfortunately, we in the United States have this dubious distinction.

No discussion of health trends in the United States should overlook the fact that in terms of health status, we have the equivalent of a developing country within our borders. By calculating county-specific life expectancies at birth in the United States, by race, the DALY re-

TABLE

Estimated Leading Causes of Disability-Adjusted Life-Years (DALYs) in the United States in 1996 (in millions)

	DALYs			**Deaths**		
	Total	men	women	Total	men	women
All Conditions	34.2	18.3	15.9	2.31	1.16	1.15
Ischemic heart disease	3.15	1.97	1.18	0.54	0.29	0.25
Unipolar major depression	1.55	0.48	1.07	(37)[a]	(12)[b]	(25)[c]
Cerebrovascular disease	1.51	0.67	0.84	0.16	0.06	0.1
Road traffic collisions	1.39	0.93	0.46	0.04	0.03	0.01
Lung, trachea, bronchus cancers	1.36	0.81	0.55	0.17	0.10	0.07
Alcohol abuse and dependence	1.15	0.74	0.41	0.0066	0.0052	0.0014
Chronic obstructive pulmonary disease	1.06	0.55	0.51	0.10	0.05	0.05
Diabetes mellitus	0.96	0.46	0.50	0.06	0.03	0.03
Osteoarthritis	0.93	0.41	0.52	(690)[d]	(182)[e]	(508)[f]
Dementia and other degenerative and hereditary central nervous system disorders	0.89	0.38	0.51	0.04	0.01	0.03

a, b, c, d, e, f: the integer shown within the parenthesis is the number of deaths recorded.
Modified, with permission, from data of Michaud CM, Murray CJL, Bloom BR. Burden of disease — implications for future research. JAMA 2001; 285:535–539 (12).

searchers found a range in life expectancies that shows how unevenly distributed our health status progress really is.

In four contiguous counties in South Dakota, the life expectancy for American Indian males is 56.51 years, which is comparable to the life expectancy for men in countries like Bangladesh and the Sudan (13).

The good news is that some counties and subgroups have unusually high life expectancies. Asian females in Bergen County, New Jersey, for example, have life expectancies of 97.72 — very close to a century of life expectancy (14).

Cardiovascular Disease

Reductions in cardiovascular disease deaths represent one of the most dramatic public health accomplishments of the last century. Between 1972 and 1992, death rates from heart disease plunged by 51%, but coronary heart disease is still the leading cause of death in the United States (15). The decrease was driven by combinations of screening, education, cholesterol and blood pressure medications, dietary changes, and exercise regimens.

Because the risk factors for cardiovascular disease — smoking, diets high in saturated fats, and physical inactivity — are increasing in developing countries, we can expect these habits to lead to increased cardiovascular disease rates decades down the road.

India, for example, already accounts for 17% of global CVD deaths (16). Between 1985 and 2025, deaths attributed to circulatory system diseases in India are expected to increase by 103% in men and by 90% in women. During a recent trip to India, I met with a cardiologist who was seeing these trends first-hand in his own practice. He told me that he could easily do 50 angiograms a day and as many coronary artery bypass grafts, just on the patients referred to him. He believed that his patients' high-fat diets, low physical activity levels, and high smoking rate — especially among men — might be combined with some type of genetic susceptibility for heart problems.

The data bear him out — at least on the fat consumption trends. Affluent Indians — who are estimated to be 5% of the population — consume 40% of the fat consumed by the entire population, mainly in the form of ghee (clarified butter) and other edible oils. Of course, 5% of India's population is 40 million people at risk of serious health problems. As India accelerates its industrialization and development, my cardiologist friend's concern is further justified.

A Focus on Solutions

As diseases and risk factors converge around the world, we will have to recognize our interdependencies and look to each other for solutions. We know that a nipavirus outbreak in Malaysia has implications for hog farms in North Carolina. Effective tuberculosis control in India and Mexico affects TB rates in the United States, as does Dengue fever control in Mexico and the Caribbean. Foodstuffs contaminated with pathogens or pesticides can originate abroad and appear on your kitchen counter.

And just as microbes and trends from outside our borders affect us here at home, so do our actions and policies affect the rest of the world — and not always for the better, as I have noted. Our pressure on the tobacco industry here in the United States has immediate ramifications for the health systems and economies of developing countries. The impact of violent American television programming is felt all over the world.

By the same token, as I noted earlier, we do know what we have to do to reverse these trends. It is not a mystery; not a realm of scientific discovery yet to be revealed. We need to continue to learn from successes elsewhere, as we have from the Finns in North Karelia. The directly observed therapy to treat tuberculosis that we use in New York City today began in Chennai, India; the Australians have been leaders in developing skin cancer prevention programs for their sun-loving, fair-skinned population.

The types of solutions we must support here and abroad have much in common — just as the risk factors faced by Americans, Finns, Thais, and Indians and everyone else are increasingly similar.

Around the world, health promotion and health education, social marketing, creative applications of new technology, and strong regulatory and political action hold promise for reversing these trends and preventing unnecessary deaths and diminished quality of life.

We have had significant successes in promoting healthy behaviors. When I trained at Mount Sinai 30 years ago, attending rounds were smoke-filled events — which is certainly not the case today.

When Archibald MacLeish saw photos of the earth projected from the first trip to the moon, he was inspired to write (17):

> To see the earth as we now see it,
> small and blue and beautiful in that eternal
> silence where it floats,
> is to see ourselves as riders on the earth
> together. . . .

We are indeed riders on the earth together. Distance no longer confers the protection it once did. Even in vastly different economic circumstances, the countries of the world seem to be pulled to a powerful magnetic north in which we are more alike, in causes of death and of DALYs, than we are different. This should serve to make us all healthier as we multiply our efforts as clinicians, researchers, and public health professionals toward these common goals.

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Role of Stathmin in the Regulation of the Mitotic Spindle:

Potential Applications in Cancer Therapy

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Abstract

Stathmin is a member of a novel class of microtubule-destabilizing proteins that regulate the dynamics of microtubule polymerization and depolymerization. Stathmin promotes microtubule depolymerization during interphase and late mitosis. This microtubule depolymerizing activity of stathmin is regulated by changes in its level of phosphorylation that occur during cell cycle progression. These modifications allow it to play a critical role in the regulation of the dynamic equilibrium of microtubules during different phases of the cell cycle. Stathmin is expressed at high levels in a wide variety of human cancers. Inhibition of stathmin expression in malignant cells interferes with their orderly progression through the cell cycle and abrogates their transformed phenotype. Thus, stathmin provides an attractive molecular target for disrupting the mitotic apparatus and arresting the growth of malignant cells. In this review, we describe the current understanding of the role of stathmin in the regulation of the mitotic spindle and discuss its potential as a therapeutic target of cancer therapy.

Key Words: Stathmin, mitotic spindle, microtubule depolymerization, cancer therapy.

WHEN A CELL DIVIDES into two daughter cells, the chromosomes must segregate prior to cell division. This process of chromosome segregation is mediated by a complex structure known as the "mitotic spindle," which is composed primarily of microtubule polymers consisting of a/b tubulin heterodimers. The movement of chromosomes on the mitotic spindle is dependent on the dynamic instability of microtubules, a characteristic property of microtubules that allows them to switch abruptly between states of elongation and rapid shortening (1). The transition from a state of growth to a state of shrinkage is called "catastrophe" and the transition from a state of shrinkage to a state of growth is called "rescue" (1). The dynamics of microtubule polymerization and depolymerization during the cell cycle are regulated by a balance between the activities of two major classes of proteins, the microtubule-stabilizing and -destabilizing proteins (1, 2). The former class is exemplified by the classic superfamily of microtubule-associated proteins (MAPs), which stabilize the assembled microtubules by suppressing catastrophe (2). The latter class is exemplified by stathmin (3), the KinI family of kinesin-related-proteins (XKCM1 & XKIF2) (4) and the microtubule-severing proteins (katanin, p56 and EF1α) (5, 6). All these proteins can destabilize the assembled microtubules by increasing the catastrophe rate of the polymers. These two classes of cellular polymerizers and depolymerizers of microtubules play a critical role in the control of cell division. Recent advances in the molecular understanding of the role of these proteins in cell cycle progression and mitotic spindle assembly provide new opportunities for designing novel therapeutic strategies. For example, perturbation of expression of such microtubule-regulatory proteins might be used to disrupt the mitotic apparatus and arrest the growth of malignant cells. A number of currently available chemotherapeutic agents such as vincristine, vinblastine and Taxol® (paclitaxel) exert their antitumor effects by disrupting the normal regulation of the mitotic spindle. This review focuses on the current understanding of the role of

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stathmin in the regulation of the mitotic spindle, and its potential as a novel target for cancer therapy. We also highlight some recent preclinical findings that may one day be translated into more effective cancer therapy.

Functional Identification of Stathmin as a Microtubule Regulator During Cell Cycle Progression

Although stathmin was discovered more than a decade ago, its precise function has been elucidated only in the last five years. The initial clue that stathmin may play a role in mitotic progression came from genetic studies that involved either antisense RNA inhibition or forced overproduction of stathmin in leukemic cells. Studies from our own group and others showed that antisense inhibition of stathmin expression results in a marked decrease in the rate of proliferation of K562 erythroleukemic cells and their accumulation in the G2/M phases of the cell cycle (7, 8). Surprisingly, overproduction of stathmin in leukemic cells also resulted in growth inhibition and accumulation of cells in the G2/M phases of the cell cycle (8). These studies suggested that cells have difficulty completing mitosis whenever the level of expression of stathmin is altered. These seemingly paradoxical findings of mitotic arrest with both antisense RNA inhibition and overproduction of stathmin were later explained by a study by Belmont and Mitchison that identified stathmin as a cellular factor that promotes microtubule depolymerization by increasing the rate of catastrophe (3). Thus, it is not surprising that either an increase or decrease in the level of stathmin expression would result in a mitotic arrest. Since the major role of stathmin in mitosis is to promote microtubule depolymerization, inhibition of stathmin should result in increased microtubule polymerization and overexpression of stathmin should result in decreased microtubule polymerization. These predictions were verified experimentally in recent studies by different groups, including our own, by demonstrating increased microtubule polymerization in cells that are deficient in stathmin (9–11) and decreased microtubule content in cells in which stathmin is overexpressed (12).

Regulation of the Microtubule Depolymerizing Activity of Stathmin During Cell Cycle Progression

The microtubule depolymerizing activity of stathmin is regulated by changes in its phosphorylation that occur during cell cycle progression (12–14). The level of phosphorylation of stathmin is significantly increased in the mitotic phase of the cell cycle relative to interphase (7). Stathmin is phosphorylated *in vivo* on four distinct serine residues (Ser16, Ser25, Ser38 and Ser63) by different protein kinases, which include cyclin-dependent 2 (cdc2) kinase (7, 15, 16), mitogen-activated protein kinase (17), calmodulin-dependent kinase (18) and cyclic AMP-dependent kinase (16, 19). Phosphorylation of all four serines in mitosis switches off stathmin microtubule-depolymerizing activity and allows the assembly of the mitotic spindle at the onset of mitosis (12). This was demonstrated by Marklund et al., who studied the effects of overexpression of wild-type and cdc2 kinase target site deficient mutants of stathmin on the morphology of the mitotic spindle (12). These studies showed that induced expression of wild-type stathmin results in depolymerization of microtubules in interphase (12). When such cells enter mitosis, stathmin is inactivated by phosphorylation, allowing tubulin to polymerize and assemble the mitotic spindle (12). In contrast, when stathmin mutants that are mutated at kinase target sites are expressed, the cells fail to phosphorylate stathmin, and microtubules can polymerize and form a functional mitotic spindle (12). These observations revealed that inactivation of stathmin by phosphorylation is essential for formation of the mitotic spindle and progression through the cell cycle (12). In a more recent study from our laboratory, dephosphorylation of stathmin by an okadaic acid-sensitive protein phosphatase was found to be necessary for the disassembly of the mitotic spindle, exit from mitosis and entry into a new cycle (10). A general scheme of regulation of polymerization and depolymerization of microtubules during the cell cycle by stathmin phosphorylation is illustrated in Fig. 1. The unphosphorylated stathmin in late interphase promotes depolymerization of microtubules, and phosphorylation of stathmin early in mitosis downregulates the microtubule depolymerizing activity allowing the mitotic spindle to form. Dephosphorylation of stathmin by an okadaic acid-sensitive protein phosphatase during late mitosis is necessary for spindle disassembly and exit from mitosis. When cells enter a second division cycle, they repolymerize their microtubules in interphase and then depolymerize them again as they enter mitosis. It is not clear yet how the polymerization and depolymerization of microtubules is regulated during interphase.

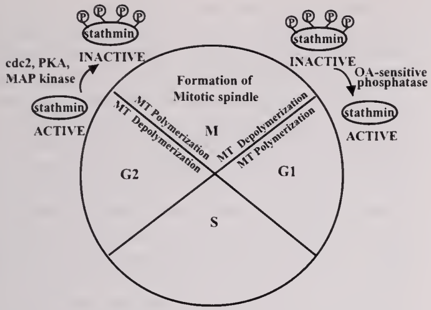
stathmin
INACTIVE
cdc2, PKA, MAP kinase
stathmin
ACTIVE
stathmin
INACTIVE
OA-sensitive phosphatase
stathmin
ACTIVE
Formation of Mitotic spindle
MT Polymerization
MT Depolymerization
M
MT Depolymerization
MT Polymerization
G2
G1
S

Fig. 1. Regulation of stathmin activity during cell cycle progression. The unphosphorylated form of stathmin in late interphase promotes depolymerization of microtubules, and phosphorylation of stathmin early in mitosis turns off its activity, allowing the mitotic spindle to form. Dephosphorylation of stathmin by an okadaic acid (OA)-sensitive protein phosphatase during late mitosis is necessary for spindle disassembly and exit from mitosis. PKA = protein kinase A; MAP = microtubule-associated protein; cdc2 = cyclin-dependent 2. M, G1, G2, and S are phases of the cell cycle.

Mechanism(s) of Stathmin-Induced Microtubule Destabilization

At least three major models have been proposed to explain the mechanism(s) by which stathmin destabilizes microtubules (Fig. 2). In the first model, proposed by Belmont and Mitchison, stathmin destabilizes microtubules by increasing the rate of catastrophes (Fig. 2A) (20). A subsequent study by Curmi et al. suggested that stathmin slows elongation but does not act directly on microtubule ends to promote catastrophes (21). The same group also showed that stathmin interacts with two molecules of dimeric α/β-tubulin to form a tight ternary T2S complex (22). This group proposed an alternative model in which stathmin destabilizes microtubules by acting as a tubulin-sequestering protein via the formation of the T2S complex, thus depleting the pool of tubulin available for polymerization (Fig. 2B) (22). These discrepancies were later resolved by Howell et al., who showed that stathmin can have two different functional activities that are compatible with both models under different pH conditions (23). They analyzed truncated stathmin lacking either a C-terminal region or an N-terminal region and showed that different regions of stathmin promote different activities (23). Another study by Larsson et al. demonstrated that stathmin mediates multiple-region-specific tubulin and microtubule regulatory activities (24). These observations led to a third model, in which stathmin mediates at least two distinct activities: a catastrophe-promoting activity, which requires the N-terminal region of stathmin, and tubulin-sequestering activity that requires the C-terminal region of stathmin (Fig. 2C) (23, 24). More recently, the same group examined the effects of N- and C-terminal truncated mutants of stathmin on interphase microtubules and mitotic spindle microtubules (25). They showed that the catastrophe-promoting activity associated with the N-terminal region of stathmin is sufficient to disrupt the mitotic spindle, while the C-terminal-associated activities are sufficient to destabilize interphase microtubules (25). This suggests that interphase and mitotic microtubules are differentially sensitive to specific activities of stathmin (25). Thus, stathmin appears to function by more than one mechanism. Despite the controversy over the mechanism(s) of activ-

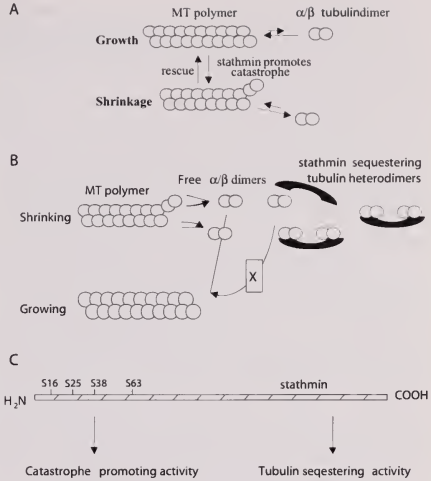
A
MT polymer
α/β tubulindimer
Growth
rescue
stathmin promotes catastrophe
Shrinkage
B
stathmin sequestering tubulin heterodimers
Free α/β dimers
MT polymer
Shrinking
X
Growing
C
S16 S25 S38 S63
stathmin
H₂N
COOH
Catastrophe promoting activity
Tubulin seqestering activity

Fig. 2. Proposed models for stathmin-induced destabilization of microtubules. **(A)** Illustrates the dynamic instability of microtubules. Stathmin promotes depolymerization of microtubules by increasing the rate of catastrophe during the dynamic transitions between phases of growth and shrinkage. **(B)** Illustrates the tubulin-sequestering activity of stathmin. Stathmin (shown by the curved bars) binds to two molecules of tubulin heterodimer, thereby depleting the pool of tubulin available for polymerization. **(C)** Illustrates the dual activity of stathmin. The N-terminal region promotes catastrophe-promoting activity and the C-terminal region promotes tubulin-sequestering activity.

ity of stathmin, there is consensus that stathmin promotes depolymerization of microtubules and is one of the key regulators of cell division.

Stathmin Overexpression in Cancer Cells

Stathmin attracted the attention of many investigators because of its high level of expression in many types of cancer. High levels of expression of stathmin have been observed in a wide variety of human malignancies, including leukemia/lymphoma (26, 27), prostate carcinoma (28), ovarian carcinoma (29), and breast carcinoma (30). The high level of stathmin expression was recently shown to correlate with established prognostic factors in breast carcinoma (31). A previous study from our laboratory showed that antisense inhibition of stathmin expression results in abrogation of the transformed phenotype of leukemic cells *in vitro* and inhibition of tumorigenicity of leukemic cells *in vivo* (32). These findings suggest that high levels of stathmin expression are necessary to maintain the transformed phenotype of leukemic cells.

Although numerous studies have demonstrated high levels of stathmin expression in cancer cells, stathmin does not seem be directly involved in the process of malignant transformation. This was evident from another study from our laboratory that examined the effects of oncogene-mediated transformation on the level of stathmin expression in an experimental tumor model (33). Our studies showed no direct correlation between the level of stathmin expression and transformation by a wide variety of oncogenes that act through different signaling pathways (33). These findings led us to propose that the high level of expression of stathmin that is frequently observed in tumor cells may be merely a reflection of their increased proliferative activity. This is supported by another study from our laboratory that showed that a high level of stathmin is necessary for maintaining the high proliferative rate of cancer cells (32). However, if the rate of proliferation of the transformed cells is profoundly reduced by inhibiting stathmin expression, they may lose the ability to behave in a malignant fashion, as reflected by their failure to cause tumors in mice (32).

Combination of Stathmin Inhibition and Anticancer Agents

Drugs that inhibit cell division by interfering with microtubule function are widely used in cancer chemotherapy. Their principal mode of action is exerted either by their ability to bind intracellular tubulin, thereby inhibiting the microtubule assembly and arresting cells in mitosis (e.g., vinca alkaloids), or promoting the assembly of microtubules and stabilizing tubulin polymers by preventing their depolymerization (e.g., Taxol®) (34). A number of chemotherapeutic drugs have been examined in combination with antisense strategies that target different proteins whose expression is necessary for the malignant phenotype (35). The antitumor activities of such combinations are additive or synergistic, depending on the cellular targets of the individual therapies. Numerous studies have demonstrated additive effects of combinations in which the cellular targets of the chemotherapeutic agents were different from the targets of the antisense therapies (36, 37). In contrast, the synergistic combination of anti-stathmin therapy and microtubule-directed chemotherapy is particularly attractive, since both therapies target the same microtubule pathway and therefore could theoretically provide an effective form of cancer therapy. In a recent study, we demonstrated that anti-stathmin therapy in combination with non-microtubule-interacting drugs like 5-fluorouracil (5-FU) and doxorubicin results in an additive growth inhibitory effect (38). In contrast, anti-stathmin therapy chemosensitizes K562 leukemic cells to the antitumor effects of Taxol® and results in a synergistic growth inhibitory effect *in vitro* (38). The synergistic combination of Taxol® and anti-stathmin therapy may provide an effective therapeutic approach that would not be associated with the severe toxicities that result from the use of multiple chemotherapeutic agents with overlapping toxicity profiles.

Future Directions

Given its role in the regulation of mitotic spindle and the dependence of transformed cells on its high level of expression, stathmin provides an attractive molecular target for gene therapy of cancer. Perturbations of expression of proteins like stathmin may disrupt the dynamic equilibrium of microtubule polymerization/depolymerization and induce apoptosis of malignant cells. The discovery of synergistic effects of the combination of Taxol® and anti-stathmin therapy *in vitro* is quite intriguing. If these *in vitro* findings are confirmed in an animal model *in vivo*, it may be possible to extrapolate this novel therapeutic approach to the treatment of human cancer. However, the success of such an approach depends on the ability to effectively inhibit stathmin expression in the vast majority of cancer cells.

Since stathmin is expressed at very high levels in cancer cells, an anti-stathmin ribozyme-based strategy may be more effective than conventional antisense strategies. Unlike antisense RNA that at best acts stoichiometrically, ribozymes can catalytically cleave multiple target RNA molecules (39, 40). We recently demonstrated the ability of three hammerhead anti-stathmin ribozymes that we designed to cleave synthetic stathmin RNA in a catalytic manner (41). We also showed that these anti-stathmin ribozymes are capable of selective cleavage of native stathmin mRNA when present in a mixture of total RNA isolated from leukemic cells (41). Adenoviral delivery systems aimed at efficient gene transfer of anti-stathmin ribozyme in cancer cells may provide a novel and effective form of cancer gene therapy. Whereas retroviral-mediated gene transfer results in the stable integration of the transgene in the transduced cell, adenovirus gene transfer systems induce an immune response in the host that results in the clearance of transduced cells (42). Although transient expression has obvious limitations for the gene therapy of genetic disease, it may be advantageous for anticancer gene therapy, since elimination of transduced cells is the major aim of such therapy. It may also be possible to combine adenovirus-mediated anti-stathmin ribozyme therapy with pharmacological therapy with Taxol®, to obtain a more potent antiproliferative and antitumor effect. Another avenue of pharmacologic intervention that should be explored is the development of small-molecule inhibitors that block the interaction between stathmin and tubulin. Since stathmin is expressed at very high levels in essentially all types of transformed cells, such therapeutic approaches may find application in the treatment of a wide range of human cancers. The studies that have been conducted so far provide proof of the principle that stathmin could be an excellent target for cancer therapy. More studies are needed before these observations can be translated into effective therapy for human cancer.

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Interesting Clinical Case Studies Involving Secondary Causes of Hypertension

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Abstract

While essential hypertension is very prevalent, secondary hypertension does occur in clinical practice with sufficient frequency to warrant special attention being given to those patients with severe hypertension who do not respond to standard treatments. The evaluation, diagnosis and treatment of secondary hypertension pose interesting challenges to the physician. In this article, three patients are described with different secondary causes of hypertension.

Key Words: Hypertension, pheochromocytoma, hyperaldosteronism, renal artery stenosis.

Introduction

Although essential hypertension is by far the most frequently encountered form of hypertension, occurring in more than 95% of patients, secondary causes of hypertension should be investigated in patients whose age, history, physical examination, severity of hypertension or initial laboratory findings suggests such causes (1). In addition, secondary causes of hypertension may be suspected in patients whose onset of hypertension is sudden, whose blood pressures are not responding to usually adequate (e.g., intermediate-to-high doses of three medications) therapy, and whose previously well-controlled hypertension suddenly becomes difficult to control (2). The following cases from the files of the Hypertension Section of the Zena and Michael A. Wiener Cardiovascular Institute during the interval from May 2000 to May 2001 illustrate some of the diagnostic and therapeutic challenges of secondary hypertension.

Case 1

A 50-year-old man with history of Crohn's disease had normal blood pressure (130/80 mm Hg) 8 weeks prior to his initial consultation, at which time he complained of recurrent frontal headaches and blood pressure as high as 224/137 mm Hg. There was a history of hyperlipidemia and a family history of premature coronary artery disease. On atenolol, amlodipine and hydrochlorothiazide, blood pressure was 186/110 mm Hg. Examination of the fundi showed retinal arteriolar abnormalities. A left-sided periumbilical abdominal bruit was heard. Urinalysis revealed the pH to be 5.0, specific gravity of 1.020, and no protein, glucose or cells. Plasma values for sodium and potassium were 138 meq/L and 4.7 meq/L respectively. The blood urea nitrogen and serum creatinine were 34 mg/dL and 2.3 mg/dL respectively. It was noted that the serum creatinine had been reported to be 1.7 mg/dL 8 weeks earlier. Supine plasma renin activity was 11 ng/mL/hr (normal < 2.33 ng/mL/hr). Based on this clinical presentation, renal artery stenosis was suspected.

Table 1 summarizes the most common clinical findings associated with renal artery stenosis (RAS). In a non-selective, or general popu-

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TABLE 1

Most Common Clinical Findings Associated with Renal Artery Stenosis

Hypertension
- Abrupt onset of hypertension < age 50 (fibromuscular dysplasia)
- Abrupt onset of hypertension > age 50 (atherosclerotic RAS)
- Accelerated or malignant hypertension
- Refractory hypertension (not responsive to therapy with ≥ 3 drugs)

Renal abnormalities
- Unexplained azotemia (atherosclerotic RAS)
- Azotemia induced by treatment with ACE-inhibitor
- Unilateral small kidney
- Unexplained hypokalemia

Other findings
- Abdominal bruit, flank bruit
- Severe retinopathy
- Carotid, coronary or peripheral vascular disease
- Unexplained congestive heart failure or acute pulmonary edema

RAS = renal artery stenosis; ACE = angiotensin-converting enzyme.

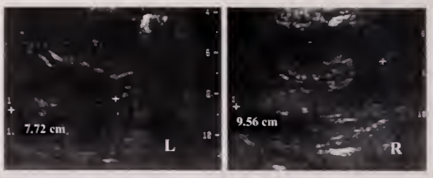

Fig. 1. Renal ultrasound of the left kidney (left panel) and right kidney (right panel). Both kidneys are normal in position. The right kidney measures 9.6 cm in length. The left kidney measures 7.7 cm in length. There is generalized loss in cortex on the left kidney. Cortical thickness on the left side measures 1 cm in thickness. The right kidney cortex measures 2 cm in thickness. There are no cystic or solid renal masses. The collecting systems are not hydronephrotic. There is no evidence for calculi in the collecting systems and there are no perinephric collections.

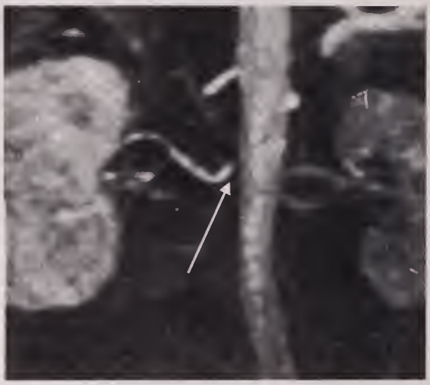

Fig. 2. Gadolinium-enhanced magnetic renal arteriogram of the aorta and renal arteries. The arrow points to a severe ostial stenosis of the left renal artery. While the left kidney is smaller than the right kidney on ultrasound (see Fig. 1), the fact that it does not appear smaller is an artifact due to clockwise rotation of the patient to bring his left side closer to the camera.

lation, of hypertensive patients the prevalence of RAS is approximately 1%. However, in selected groups, the prevalence may be significantly higher. In one study of 505 hypertensive patients, the prevalence of renal artery stenosis was 42 – 55% (3) in those patients whose hypertension was refractory to three antihypertensive medications, whose diastolic hypertension exceeded 110 mm Hg, and whose hypertension was associated with signs and symptoms of generalized atherosclerosis (e.g., coronary artery disease and/or intermittent claudication). Prevalence of RAS also increased in those individuals younger than 40 years with severe hypertension, in those in whom an abdominal bruit was heard, and in those whose serum creatinine level increased by at least 0.23 mg/dL while being treated with angiotensin-converting enzyme (ACE) inhibitor.

A renal ultrasound on this patient (Fig. 1) showed asymmetry of renal size, with some loss of renal architecture on the left side. This finding, in conjunction with the elevated plasma renin and serum creatinine, suggested significant stenosis of the left renal artery. Doppler ultrasound was not done at the time of renal ultrasound. To avoid possible renal toxic effects of intravenous contrast media, the patient underwent a magnetic resonance arteriogram (MRA). The MRA (Fig. 2) confirmed the presence of severe ostial left renal artery stenosis consistent with atherosclerotic renal artery disease.

Non-invasive renal artery imaging has become an important tool in the work-up of RAS. In general, atherosclerotic renal artery stenosis and hypertension in most elderly patients is not renin-dependent. The results of functional tests, such as renal captopril scanning, do not predict who will have a decrease in blood pressure as a result of surgical revascularization. Table 2 summarizes the current non-invasive techniques available for imaging the renal arteries.

TABLE 2
Non-invasive Imaging of the Renal Arteries

Method	Images of Vessels	Tissue Perfusion	Function GFR	Comments
Captopril renogram	–	+++	++	Change in GFR with captopril estimates reversibility. Advantages: widely available, normal study makes significant vascular disease unlikely.
Contrast angiography	+++	++	±	Gold standard. Nephrogram estimates volume of viable tissue. Disadvantages: risk of catheter and contrast.
Duplex ultrasound	++	++	–	Advantages: precise measure of flow velocity, suitable for serial studies, relatively inexpensive. Disadvantages: little functional information, not suitable for accessory vessels.
MRA	++	++	±	Accuracy limited to proximal vessels. Advantages: nontoxic in setting of advanced renal failure. Disadvantages: little functional information, not suitable for accessory vessels.
Spiral CT	+++	+	±	Advantages: good 3-D angiography images, including venous structures, possibly suitable for transplant donor evaluation. Disadvantages: large quantity of contrast media needed, demanding breath holds.

GFR = glomerular filtration rate; MRA = magnetic resonance arteriogram; CT = computed tomography.

A renal arteriogram was performed on this patient; it confirmed the ostial stenosis. A stent was placed in the obstructed artery. However, after its placement, there was no filling observed distally in the kidney. The patient was brought emergently to the operating room. The surgeons observed that the renal artery was occluded immediately distal to the stent at a point of dissection. A hepatorenal artery bypass was performed with a saphenous vein graft placed between the hepatic artery and the two large branches at the bifurcation of the renal artery. Postoperatively, hypertension did persist but fewer medications were required to achieve adequate control.

Balloon angioplasty was initially introduced as a potential cure for hypertension in patients with RAS. Dramatic success was observed in patients with fibromuscular dysplasia, with 78% of patients achieving either blood pressure less than or equal to 140/90 mm Hg or a decrease in diastolic blood pressure of at least 15 mm Hg (4). Poor success, however, is seen in patients with atherosclerosis, due to high rates of dissection, elastic recoil and technical problems with rigid lesions (5). Aurell and Jensen reported a 19% technical failure rate with atherosclerotic renal artery stenosis, and up to 65–70% failure with ostial lesions (4). Placement of intrarenal artery stents has more potential for success in ostial renal artery stenosis. In a study of patients who underwent stenting due to failure of initial angioplasty, restenosis of more than 50% occurred in 11% of arteries (5). When angioplasty was repeated within the stent, or when a second stent was placed, the resulting secondary patency rate was 92%. However, long-term normalization of blood pressure without antihypertensive medication was achieved in only 16% of patients. This outcome is consistent with atherosclerotic RAS. Blood pressure returns to normal values in 78% of the patients with fibromuscular dysplasia. Thus, as with atherosclerosis of the coronary arteries, many older patients with atherosclerotic RAS may respond favorably to treatment with ACE inhibitors and lipid-lowering agents.

Long-term survival after surgical bypass, as with the patient described above, is good. One study of surgical outcomes reported long-term cure or improvement in blood pressure in 72% of 222 patients and stabilization of renal function in 71% of patients (6). While our patient's serum creatinine decreased to 1.9 mg/dL, indicating some slight renal functional improvement, his blood pressure only decreased somewhat, to 164/92 mm Hg. However, satisfactory blood pressure control was achieved on a regimen of an ACE inhibitor and a thiazide diuretic.

Case 2

A 29-year-old woman was seen on the surgical service because a sudden increase in her blood pressure to 200/130 mm Hg had been noted upon induction of anesthesia for a surgical procedure on her right foot. A series of surgical procedures had been in progress to re-implant the right foot which had been severed during an accident. Similar blood pressure elevations had been documented previously. Transient blood pressure elevations continued for several days postoperatively and were associated with palpitations, dizziness, diaphoresis, nausea, vomiting and significant feelings of anxiety. The patient had been experiencing similar symptoms from time to time over the past several years. Upon examination, the first recorded blood pressure was 120/90 mm Hg with a pulse rate of 84 beats per minute (bpm). During the examination, she developed typical symptoms. Her blood pressure and heart rate increased to 160/90 mm Hg and 108 bpm. Symptoms resolved after several minutes and her blood pressure and pulse rate returned to baseline values. The rest of the examination was unremarkable. Urine catecholamine metabolites (on no medication) were as follows: urinary homovanillic acid (U-HVA) 3.0 μg/mg creatinine (normal 0.0–2.5); urinary vanillylmandelic acid (U-VMA) 6.00 μg/mg creatinine (normal 0.25–3.50). Blood cell counts, blood chemistries and urinalysis were normal. A magnetic resonance image (MRI) of the abdomen showed a 2.2 × 1.9 cm nodule in the right adrenal gland. The nodule was well circumscribed and homogeneous, and was isointense to the spleen on in- and out-of-phase T1-weighted gradient echo images (Fig. 3). The clinical findings suggested a pheochromocytoma. The clinical features of pheochromocytoma are outlined in Table 3. However, the MRI findings were not typical of pheochromocytoma, since the image of the tumor appeared to be relatively less intense than the liver (7). A ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) was performed to assess whether the adrenal mass sequestered and stored MIBG which shares the same uptake, storage and release mechanisms as norepinephrine in adrenergic nerve terminals and pheochromocytomas (8). The MIBG scan

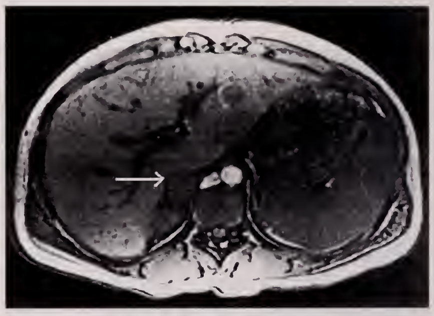

Fig. 3. Axial breath-hold T1-weighted magnetic resonance arteriogram (MRA) gradient echo image of the abdomen. The arrow shows a well-circumscribed adrenal mass.

TABLE 3
Clinical Signs of Pheochromocytoma

BP changes
- Hypertension Å fluctuations
- Hypertension induced by physical maneuver (exercise, postural change) or palpation of a mass
- Orthostatic hypotension Å postural tachycardia
- Paradoxical BP response to medication

Other signs of catecholamine excess
- Hyperhidrosis
- Tachycardia or reflex bradycardia, very forceful heartbeat, arrhythmia
- Pallor of face and upper part of body
- Anxious, frightened, troubled appearance
- Hypertensive retinopathy
- Dilated pupils
- Leanness or underweight
- Tremor ± shaking
- Raynaud's phenomenon or livedo reticularis
- Fever

Mass lesion (rarely palpable)

BP = blood pressure.

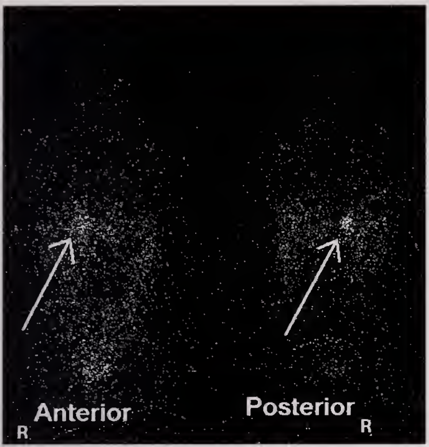

Fig. 4. Focal uptake of I^{131}-metaiodobenzylguanidine (I^{131}-MIBG) on anterior and posterior whole body views in the region of the right adrenal gland, confirming that the adrenal mass is a catecholamine-producing tumor.

showed focal increased MIBG uptake in the region of the right adrenal gland (Fig. 4). Thus, the adrenal mass seen in the MRI was interpreted to be a pheochromocytoma.

In a recent National Institute of Health (NIH) conference on pheochromocytoma, sensitivities and specificities of the common blood and urine tests were reported, as outlined in Table 4 (10). If the initial biochemical tests are not diagnostic, other functional tests may be performed. The most common is the clonidine suppression test. This test is useful for distinguishing between high levels of plasma norepinephrine caused by release from sympathetic nerves (suppressed by clonidine) vs. those caused by release from a pheochromocytoma (not suppressed) (9). For diagnostic localization of pheochromocytoma, computed tomography (CT) and MRI both have overall good sensitivity (93–100%), but somewhat poor specificity (as low as 50%). MIBG scanning has 95–100% specificity, but has lower sensitivity (77–90%) than CT and MRI (10).

The treatment of choice for this patient with a pheochromocytoma was surgical resection of the mass. She was admitted to the intensive care unit preoperatively for medical stabilization. Medical control before surgery leads to better control of blood pressure and decreased surgical risk. Metyrosine was used to reduce tumor stores of catecholamines and to decrease the need for intraoperative medication to control wide swings in blood pressure and excessive losses of blood. Alpha-adrenergic receptor blockade was achieved with phenoxybenzamine administered intravenously, along with intravenous esmolol, a beta blocker. The traditional surgical approach is by transabdominal incision, and is associated with a 97.7–100% survival rate and residual non-paroxysmal hypertension in 27–38% of patients (10). However, our patient underwent laparoscopic surgery. This approach has similar blood loss and complications, but less postoperative pain, shortened hospital stay and convalescence with improved cosmetic result (10). This patient was discharged 24 hours after surgery. She has had no further symptoms or elevated blood pressure readings.

Fig. 5 (left side) shows the resected adrenal gland and the pheochromocytoma with areas of mild hemorrhage enclosed within an attenuated adrenal cortex. The residual adrenal gland is also seen as a small “tail” on the right side of the mass. The right panel shows the histologic pattern with normal rim of adrenal cortex (left edge) adjacent to tumor. The histologic pattern

TABLE 4

Sensitivity and Specificity of Biochemical Tests for the Diagnosis of Pheochromocytoma

Biochemical Test	Sensitivity (%)	Specificity (%)	Sensitivity at 100% Specificity (%)
Plasma metanephrine	99	89	82
Plasma catecholamine	85	80	38
Urine catecholamine	83	88	64
Urine metanephrine	76	94	53
Urine vanillymandelic acid	63	94	43

The sensitivities at 100% were determined by increasing the upper reference limits for each test to levels at which no patient without a pheochromocytoma had a positive test result. Sensitivity was determined for tests in 151 patients, and specificity was determined for tests in 349 patients. This indicates the percentage of patients with pheochromocytoma in whom test results are so high that they unequivocally confirm the presence of pheochromocytoma. See reference 10.

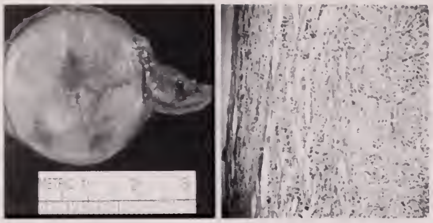

Fig. 5. Gross (left) and histologic (right) sections of the adrenal tumor. (H&E stain, 10x).

is variable with polygonal to spindle-shaped chromaffin cells, clustered with their supporting cells into small nests or alveoli (zellballen) with a rich vascular network (11). The histologic pattern, however, does not predict malignancy, which must be based exclusively on the presence of metastases (12).

Case 3

This 76-year-old woman was known to have hypertension for one year. Upon presentation to her physician for visual disturbance, blood pressure was 204/102 mm Hg. There was no evidence of stroke or transient ischemic attack by physical examination or by CT of the head. She was taking 75 mg atenolol and 12.5 mg hydrochlorothiazide, and her blood pressure in the clinic was 180/84 mm Hg, Daytime blood pressure was 140/73 mm Hg and nighttime blood pressure was 149/79 mm Hg by ambulatory monitoring. With the addition of 10 mg amlodipine, there was better overall control. However, there were still transient high readings by home recordings. Blood chemistries were normal with a serum potassium level of 4.0 meq/L. A supine plasma renin and serum aldosterone were 0.18 ng/mL/hr (normal 0.15 – 2.33) and 72.4 ng/dL (normal 1.0 – 16) respectively. Aldosterone-to-renin ratio was 40.2 (normal less than 25). These findings indicated hyperaldosteronism.

The quoted prevalence of primary aldosteronism is less than 1%. However, it may be as high as 12%, with significant hypokalemia only in severe cases (13). In one series, evidence of primary hyperaldosteronism (elevated aldosterone, diminished renin, elevated aldosterone/renin ratio) was observed in 29 of 305 patients (9.5%) with essential hypertension. Many of these patients had glucocorticoid-remediable aldosteronism (14).

An MRI scan of the abdomen (Fig. 6) showed hypertrophy of the left adrenal gland. The right adrenal gland appeared normal. Although an aldosterone producing adenoma (APA) is not visualized, the scan did not clearly establish either the diagnosis of primary adrenal hyperplasia (PAH) or idiopathic hyperaldosteronism (IHA) in which both glands are typically enlarged. Adrenal venous sampling was performed. Fig. 7 shows contrast injected into the left adrenal vein. There was no tumor blush indicative of an adenoma. Baseline aldosterone was elevated in both the right and left adrenal veins, 48.2 ng/dL and 54.2 ng/dL respectively. After infusion of adrenocorticotrophic hormone (ACTH), these values increased to 2318 ng/dL in the right adrenal vein and 5532 ng/dL in the left adrenal vein. Although higher values were noted in the left adrenal vein, the significantly high results bilaterally suggested PAH or IHA. Additional tests were performed. Baseline total cortisol, 18 hydoxycorticosterone and serum al-

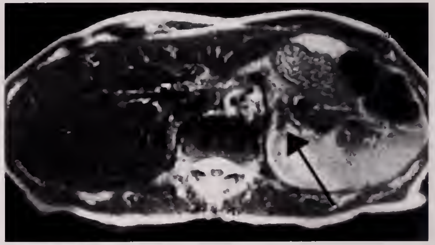

Fig. 6. Hypertrophy of the left adrenal gland (arrow). The right adrenal gland (not well visualized in this view) is normal.

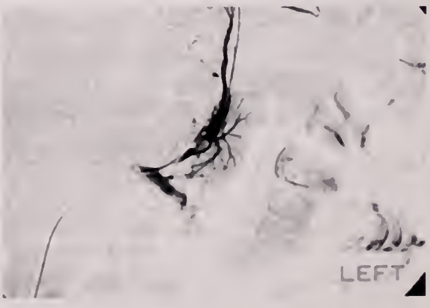

Fig. 7. Contrast injection of the left adrenal vein. No blush, usually seen with an adenoma, is evident.

dosterone were 18.2 μg/dL (normal 4–22), 76 ng/dL (normal 4–37) and 26 ng/dL (normal 2–9) respectively with an 18 hydroxycorticosterone/cortisol ratio of 4.2. After a 2-liter infusion of saline, repeat assays were 13.2 μg/dL, 32 ng/dL and 7 ng/dL respectively with 18 hydroxycorticosterone/cortisol ratio of 2.42. A ratio of less than 3 is suggestive of IHA (15). In IHA, aldosterone and 18 hydroxycorticosterone (which are renin dependent) decrease more than cortisol in response to saline volume expansion. Cortisol is influenced only by the circadian rhythm of ACTH, whereas aldosterone and 18 hydroxycorticosterone have an additional decrease when saline produces exogenous suppression of the renin angiotensin system. This does not occur with adenomas, which are less dependent on the renin angiotensin system. IHA is characterized by micro- or macronodular hyperplasia of both adrenals and rarely as unilateral disease (16). This patient was treated with antihypertensive medication and potassium-sparing diuretics. Spironolactone was the drug prescribed initially since amiloride is less likely to control blood pressure. The patient responded well to a combination of spironolactone and atenolol. A diagnostic algorithm for hyperaldosteronism is summarized in Fig. 8.

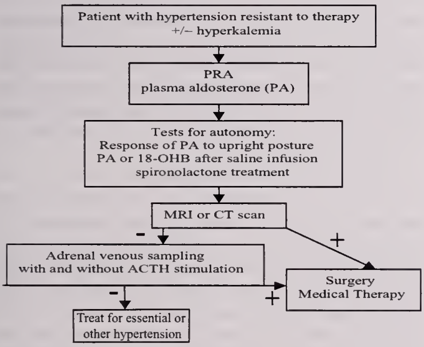

Fig. 8. Diagnostic algorithm for hyperaldosteronism. 18-OHB is 18 hydroxycorticosterone. If MRI or CT scan is negative, adrenal venous blood should be sampled to determine serum levels of cortisol, 18 hydroxycorticosterone, and aldosterone. This may be carried out with or without ACTH stimulation. If results are not diagnostic (see narrative text), treatment for essential or other hypertension should be initiated. If the MRI or CT scan is diagnostic of an adrenal lesion, or if the above-mentioned levels of steroids in adrenal venous blood are diagnostic, then either surgery or medical therapy may be appropriate.

Conclusion

The cases discussed illustrate current diagnostic and therapeutic principles in challenging cases of secondary hypertension. Although not common, secondary forms of hypertension will present in clinical practice, particularly in patients with resistant arterial hypertension. In those patients whose blood pressure remains above treatment goals despite adherence to a triple drug regimen (including a diuretic and near maximal doses of other medications), secondary causes of hypertension should be sought.

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Genetics and Education:

The Ethics of Shaping Human Identity

Vardit Ravitsky, M.A.

Abstract

This paper suggests an analogy between education and genetic interventions as means of shaping the identity of children and future adults. It proposes to look at issues discussed in the philosophy of education as a possible source of insight for ethical guidelines regarding future genetic interventions. The paper focuses on situations of conflict between parents and state regarding the authority to determine the child's best interests. It describes the current formulation of the conflict in the literature as lacking the crucial element of the child's right to a cultural identity. It argues that this element is a necessary component in an ethical analysis of the child's best interests in a multicultural, liberal society which respects diversity. The paper therefore proposes a better model for the moral evaluation of identity-shaping decisions and offers some implications of this model for genetics.

Key Words: Identity, genetic interventions, behavioral genetics, children, education, culture, liberalism, autonomy, diversity.

Introduction

The Human Genome Project, and the consequent efforts to understand the meaning of genetic information, are providing us with new choices regarding the creation of new people. As in any other field of human activity, greater choice means greater responsibility. Thus, each discovery regarding the genetic basis of a disease, a trait or a behavior, raises ethical concerns about the proper use of such information.

At present, prenatal genetic testing enables parents to have access to information about the genetic makeup of their fetus. On the basis of this information, they may decide to terminate a pregnancy. Furthermore, pre-implantation genetic screening provides potential parents who have chosen *in vitro* fertilization, with information about the various pre-embryos and enables them to select the candidate they prefer for implantation. In the future, it may become possible for parents to request direct genetic interventions in a specific pre-embryo in order to add, extract or modify pieces of DNA, with the aim of shaping the identity of their future child. Such interventions, when done not with the aim of diagnosing disease, but rather with the aim of choosing a characteristic, raise the ethical issue often referred to as the problem of "designer babies."

Much of the bioethical literature perceives the idea of parents consciously and voluntarily shaping the identity of their offspring by genetic interventions as raising new ethical concerns. However, the case of "designer babies" raises some very old ethical issues. Human beings have been shaping the identity of children for centuries, by controlling the environment in which children develop and, more directly, by educating them. I propose to think of education as the classical method of achieving the same goals that behavioral genetics will probably pursue through high-tech interventions.

The "nature vs. nurture debate," that famous competition between genetic and environmental explanations of human identity and behavior, has accompanied philosophical thought from its origins. From the days of Plato (1), philosophers have been discussing the proper way to shape the identity of future citizens,

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both in terms of genetic choice (i.e., choice of mate) and in terms of education. New insight into the role genes play in the shaping of human identity is not likely to put an end to that debate. The ethical discussion should, however, relate to the process of identity shaping as a continuous one. Any conscious, voluntary human intervention aimed at influencing that process has important ethical dimensions, whether it is genetic choice at the very beginning, or education at later stages.

Genetic determinism, which is scientifically untenable as well as ethically dangerous, is not a necessary assumption in such an ethical discussion. It is enough to accept that there is a genetic component involved in aspects of human identity such as intelligence, aggressiveness, assertiveness, submissiveness, sexual orientation, or the predisposition to addiction, to depression, or to novelty seeking. All phenotypic expressions (physical, cognitive, mental or behavioral) are the result of a complex interaction between genes, other biological factors and the environment in which the individual develops. Even though, within that complex system, the genetic factor is but one of many, there is still an important ethical dimension to any attempt to shape human identity by controlling that one factor.

One may attack this proposed analogy between education and genetic interventions by arguing that identity shaping through education is permissible insofar as it is reversible, whereas identity shaping through genetic interventions is irreversible and should therefore be prohibited. However, education and genetic interventions are both highly complex ways of influencing the development of human identity. There is no reason to assume that one will have more conclusive results than the other. Both are components in an intricate process that humans have always tried to influence or control.

The Question of Authority

Questions about the ethics of current and future genetic interventions have an important political dimension, because they raise concerns about the authority to make decisions regarding the identity of future children. How should authority be delegated between parents or families on the one hand and the state on the other, when the identity of children is at stake? In this paper I propose to look at the question of authority as discussed in the philosophy of education, as a possible source of ethical insight for the future regulation of genetic interventions. My discussion will be limited to the context of the democratic liberal state, in which public policy regarding these issues is actually developing.

I will focus on situations of conflict between parents and state, around the question of the child's best interests. What ethical considerations are involved when parents choose to educate their children in ways that the liberal state believes to be harmful to them? What is the scope of parental liberty? What justifies state interference with parental choice? Some important implications of these questions of education, I argue, are valid in the context of genetic choice as well.

Liberal theory, following in the footsteps of Locke (2), does not perceive children as the property of their parents but rather as separate and independent moral individuals. He states, "Thus we are born free as we are born rational . . . age that brings one brings with it the other, too. And thus we see how natural freedom and subjection to parents may consist together. . . ." When parents do not act in their children's best interests, the state in its traditional role of *parens patriae* (parent of the nation) intervenes on behalf of the child. The scope of parental liberty is defined around the notion of the child's best interests. State intervention is perceived as legitimate and even mandatory when risk of harm to the child is present or probable.

Defining "best interests" or "harm" thus becomes an important political issue of authority. Having the power to determine the conditions of harm means having the power to justify state interference with the private sphere of parental autonomy. In the context of multiculturalism, in a social reality of diversity, where different cultures and value systems are competing, the concept of harm may be understood in many different ways. The question of authority becomes, therefore, central to the debate.

Autonomy-Based Liberalism

A classical liberal answer to the question of the child's best interests, rooted in Locke's theory of education, is provided by the notion of "personal autonomy." It says that growing up to become an autonomous adult is the child's main best interest, so that an education which does not promote autonomy is harming the child. Raz (2) states it simply, when he discusses the way liberal states should treat non-liberal cultures within them:

> One particular troubling problem concerns the treatment of communities whose culture does not support autonomy. . . . Since they insist on bringing up their children in their own ways they are, in the eyes of liberals like myself, harming them.

According to this view, if parents choose education which does not promote future autonomy, the state has a moral obligation to intervene. Possible examples are those of the education provided by the Amish or the Jewish ultra-orthodox community. Children raised within these communities may find later in life that they are unable to get into college or find employment outside of their communities.

In Raz's terms, their autonomy is being diminished rather than enhanced by their education, and the state must intervene. He therefore adds: "Assimilationist policies may well be the only humane course, even if implemented by force of law." "Autonomy-based liberalism" gives the state the authority to enforce the liberal majority's view of the child's best interest as developing into an autonomous adult, on minority cultures which hold different views. Such enforcement is likely to result in the long run in the "break-up [of] their communities, which is the inevitable by-product of the destruction of their separate schools" (3).

Diversity-Based Liberalism

However, "autonomy-based liberalism," and the hierarchical conception of cultural diversity which accompanies it, is not the only possible version of liberalism. A different voice in the literature is that of "diversity-based liberalism," according to which a serious respect for diversity requires that we accept the reality that personal autonomy is valued by certain cultures and not by others. According to this view, promoting autonomy over other, competing values constitutes a serious violation of people's right to manage their lives, and to educate their children, according to their own beliefs. In Galston's words (4):

> [T]he decision to throw state power behind the promotion of individual autonomy can weaken or undermine individuals or groups that do not and cannot organize their affairs in accordance with that principle, without undermining the deepest sources of their identity.

Here again, the Jewish ultra-orthodox community provides an excellent example. Making personal autonomy an educational goal will undermine the ability of such a community to maintain its identity. Autonomy-derived ideals such as critical thinking or "being the author of one's own life-story" are not easily compatible with a culture based on the acceptance of religious authority. Therefore, in a multicultural society, in Macedo's words (5):

> That the good life consists in autonomy is properly regarded as one more sectarian view among others, no more worthy of commanding public authority than other philosophical and religious ideals of life that reasonable people might reject.

A liberal conception which is seriously committed to the protection of diversity cannot take the future autonomy of the child as an absolute standard against which all identity-shaping procedures are morally evaluated. Therefore, it leaves the authority to make identity-shaping decisions in the hands of parents and communities. But does that mean that, other than clear cases of physical abuse and neglect, there are no limits to parental freedom? If personal autonomy is not the standard against which harm is defined, what other standard can the state hold?

Elliott (6) writes:

> It is not uncommon these days for groups of human beings with a particular biological characteristic, often an illness or disability, to identify themselves as a culture or a community. In the same way that we hear of Jewish or Amish cultures . . . we now hear about Deaf culture. . . . This makes the once-familiar lines between biology, identity and culture look rather tangled.

Should parents be allowed to "choose for disability" (7) in the name of cultural compatibility? If one accepts the Deaf culture argument, and considers the Deaf community to be a valid source of cultural identity for its members (8), one should admit that the liberal state, as committed to the protection of cultural diversity, must allow parents to make a genetic choice that will ensure the birth of a deaf child, since they themselves do not perceive such a choice as harming that child. Does respect for diversity leave children completely "defenseless" against their parents' ideals of the good life? How can we provide a full account of the child's best interests in a liberal multicultural society which respects diversity while being committed to the protection of all children?

Identity Shaping and the Right to Culture

Following in the footsteps of Kymlicka (9), I would like to argue that identity does not develop in a vacuum. It is rather the result, among other things, of a process of socialization which occurs within a specific cultural context. People have the right to belong to a culture (10), the right to be embedded in the social context of a community, because only in such a context can they give meaning and value to their lives, and evaluate the different options available to them. Cultures provide the environment within which individuals can make meaningful choices. Personal autonomy cannot be exercised outside a cultural context, because in a moral and social vacuum the individual is unable to ascribe meaning or to assess value.

It is, therefore, misleading to think of the child as having a deep interest in becoming autonomous, or in having an "open future" (11), without giving enough weight to the child's interest in belonging to a culture. And in order to be culturally embedded, a child must go through a long and complex process of education and socialization. In other words, for a child to exercise her right to a culture as an adult, her parents must create a cultural context during her formative years.

Since children are born into families, they are also born into given cultures, and a strong argument can be made in favor of their right to become embedded in those cultures. Other options involve either the removal of children from their organic families, and as Gutmann comments (12): "liberals justifiably fear a state so powerful that it could, as a matter of routine practice, take all children away from their biological parents," or state intervention within the private sphere of family life, which must be justified on grounds of protecting the child from harm.

The Child's Best Interests: A Balanced Model

The concept of the child's best interest is of paramount importance in the liberal model. The current formulation of the dilemma in the literature (7, 11, 13) confronts the child's best interests, as perceived by the liberal majority, with the interests of his parents and the community into which he has been or will be born. However, according to this formulation a crucial element is missing from the picture. That element is the child's interest in having a cultural identity.

I would like to propose a better way of constructing the dilemma of identity-shaping, one which offers a fuller and richer account of the child's best interests: not as a conflict between the child's future autonomy and the parents' current autonomy, but rather as a conflict between two different interests that the child herself has: one, in being socialized into a cultural context that will provide her, as an adult, with a cultural identity and will give meaning and value to her life; the other, in having an open future in the sense of "cultural mobility," i.e., the ability to choose, as an adult, to leave the culture she was socialized into, and join a different one. An ethical analysis should look for a sensible and sensitive balance between these two different interests, rather than ignore an important aspect of the child's identity-shaping process.

The model I would like to propose is one in which the scope of the child's right to a cultural identity is determined by the ethical requirement of "cultural mobility" or "conditions of exit." Parents should enjoy the liberty to determine the content and the aims of children's education, as well as the liberty to make genetic choices that will shape the identity of their future children, as long as these choices do not create adults who are "trapped" within their own cultures.

Galston (4) speaks of "rights of exit" from one's original culture, in the context of adulthood: "In circumstances of genuine pluralism, individual freedom is adequately protected by secure rights of exit coupled with the existence of a wider society open to individuals wishing to leave their groups of origin." However, in the context of childhood "the classic model of voluntary association" is inadequate. Galston is aware of the fact that "we are born into certain groups to which we do not choose to belong." A child is generally incapable of leaving his group of origin, but without certain basic capacities he also will not be able to exercise his right of exit in the future.

Determining the minimal requirements for the future exercise of rights of exit becomes, therefore, the key to a properly balanced model for the protection of children's best interests. Galston mentions four necessary conditions which would make the adult's right of exit a meaningful one. To meet these conditions of exit, the process of identity-shaping must provide: (a) basic knowledge about the existence and content of other cultures; (b) the ability to evaluate other cultures and compare them to one's own; (c) basic abilities which make it possible to effectively become integrated into another culture; and (d) protection from physical or psychological coercion to remain a part of the community in the future. Each of these conditions should be grounded in adequate genetic choice, in proper education, and in a properly balanced process of enculturation.

Implications for Genetics

The implications for genetic choice are clear in the case of "choosing for disability." Just as parents should not be allowed to intentionally raise illiterate children who will not be able to become effectively integrated in other cultures, so they should not have the liberty to make genetic choices which will result in children with limited physical or cognitive abilities. Any choice that will obviously trap the future individual in her community of origin is thus impermissible.

In the context of behavioral genetics, however, the implications are more complicated. As noted earlier, future discoveries of genes which underlie not disease and disability, but rather normal variation in human behavior and personality traits, may induce parents' attempts to increase the level of control they have over the genetic makeup of their offspring.

Parents' wishes to genetically reinforce a certain personality trait or behavioral predisposition, in order to enhance the cultural compatibility of their child with the community in which she will live or with a certain set of beliefs that they hold, should be evaluated through the ethical lens of future cultural mobility. State interference is justified when genetic choice is not in the child's best interest, as determined by balancing her right to her own culture against her right to future cultural mobility.

If, for example, parents choose a genetic intervention aimed at the enhancement of aggressive behavior because they live in a warrior culture such as the fictitious Klingon culture (as depicted in "Star Trek — the Next Generation"), their choice will be ethically impermissible if as a result of it the child will never be able to successfully become integrated in a non-warrior, peace-loving culture.

Other parents, living in a patriarchal society, may wish to genetically enhance their future daughter's predisposition to submissiveness, in order to improve her chances for a "good marriage." In their own eyes, they will be acting in her best interests. However, conditions of exit require that such an intervention will not result in a woman who is submissive to the point of being unable, as an adult, to choose life in a culture based on gender equality.

Conclusion

This paper analyzed the concept of the child's best interests in the context of the liberal multicultural state. It argued for a model of evaluation in which the ethical consideration of the child's future autonomy is balanced against considerations regarding her future cultural identity, so that future cultural mobility is protected. It then offered some general guidelines for "conditions of exit" from one's culture of origin.

This proposed model for the ethical evaluation of education has important implications for the evaluation of future genetic interventions which aim to shape aspects of children's identities in order to enhance their compatibility with their parents' community and culture. As in the context of education, parental freedom to use genetic interventions should be restricted by the state if, as a result of it, the child will be unable, as a future adult, to leave his culture of origin and become effectively integrated in the culture of his choice. The proposed model thus offers a tool for the ethical evaluation of future genetic choices ranging from physical characteristics to behavioral predispositions and personality traits.

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The Doctor's Defense

Richard H. S. Tur, M.A., LL.B.

Abstract

The paper takes as its point of departure a relatively recent case which attracted publicity in Britain, concerning a doctor charged with (but acquitted of) the murder of his terminally ill patient, and critically examines the criminal law of England and Wales relating to homicide in the context of medical practice. While similar issues obviously arise in many other countries, no comparative study is attempted in the paper. However, the arguments which have been presented are of more than local interest. From an analysis of this case and others, it appears that there is in common law something which can be called "the doctor's defense." It holds that a doctor may, when caring for a patient who is suffering great pain, lawfully administer pain-killing drugs, despite the fact that, as the doctor well knows, one certain or highly probable consequence will be to shorten the patient's life.

Current justifications for this defense are either incoherent or too weak. Some require that different conceptions of "intention" be deployed, depending on whether the agent is a doctor or not. Others rely on the philosophically controversial doctrine of double effect. Still others invoke an implausible notion of minimal causation. All these justifications apply readily enough to morally and factually easy cases, but fail in hard cases where the need for some justification is most pressing. These justifications seem incapable of providing adequate guidance to prosecutors or trial judges. Absent principled and transparent justification, the English criminal justice system exhibits different outcomes on what appear to be broadly similar facts. It is disturbing that the law is uncertain and incapable of giving adequate guidance. A doctor, compelled by conscience to intervene to end a person's life, should certainly be ready and willing to face rigorous legal scrutiny, but the law applied should not be arbitrary and random, nor should the outcome turn solely or chiefly on prosecutorial discretion or the predilections of the trial judge. The hope is to find a better rationale for the doctor's defense through an analysis of professional ethics and the concept of a recourse role.

Key Words: Law, cause of death, murder, euthanasia, professional ethics.

Introduction

> "The frequently expressed view that we all know that doctors help people to die and it's all right provided they do not speak about it, is unsatisfactory." (1)

I look only at the criminal law of England and Wales as it pertains to murder and medical practice. I am, of course, aware that similar legal controversies and intellectual issues arise in other legal systems (2, 3), but I have not attempted a comparative study of practices in other jurisdictions. I take as my point of departure a relatively recent case which attracted publicity in Britain. From an analysis of that case and commentary on it (4), I conclude that there is in common law something which can be called "the doctor's defense." In view of the ambiguities in the definition of "intention"(5), and the limitations inherent in the concept of causation, my hope is to find a better rationale for the doctor's defense than those current, and to find it in professional ethics. I shall deal with these three issues in the following order: (a) causation, (b) intention, and (c) professional ethics. First, I turn to the relevant details of the case.

Dr. David Moor, a general practitioner, who apparently admitted helping up to 300 people to die (6), was charged with murdering a patient by administering a large dose of diamorphine. The murder trial commenced on April 4, 1999 and concluded with the defendant's acquittal on May 11, 1999. The jury took only 65 minutes to reach its decision.

George Liddell was a widower of 85 who had been diagnosed as suffering cancer of the bowel. He had been hospitalized, and part of his bowel had been surgically removed. This

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surgery was successful, though there was some remaining cancerous invasion of adjacent fatty tissue and also, to a very small degree, of the liver. Rightly or wrongly, the hospital concluded that the patient was sufficiently recovered and mobile to leave and live with his daughter, who was already one of Dr. Moor's patients. Mr. Liddell was treated at home by Dr. Moor and a team of experienced nurses. The patient quickly became immobile and depressed, and appeared to have considerable pain. At first it was thought that the pain was caused by severe bedsores which had developed in the hospital, but as these healed, the relatives, nurses, and Dr. Moor concluded that the pain was internal and resulted from a failure to remove all the cancer. Dr. Moor prescribed 5 mg of diamorphine to be taken at intervals, and later this dosage was doubled when the pain resurfaced. Mr. Liddell was now very emaciated and appeared to be failing rapidly, though he was still taking food and water. The nurses thought him "terminally ill." He himself thought that his time had come and said that he did not want to go on. The relatives were very caring and there was no suggestion at all that they wanted to hasten death. On one occasion, when the relatives tried to move him, Mr. Liddell cried out in pain. This was reported to Dr. Moor by a nurse, who suggested that Mr. Liddell should be admitted to a local hospice for pain assessment. Dr. Moor agreed. With the consent of Mr. Liddell's relatives an application form was completed for admission to the hospice.

At this stage Dr. Moor prescribed diamorphine at the rate of 30 mg over a 24-hour period by way of a syringe driver, and that was set up later in the day. By evening Mr. Liddell was sleeping peacefully, although Dr. Moor thought that he was near death. When he telephoned the next morning, Dr. Moor was told that Mr. Liddell was still alive but making loud retching noises in his throat. Dr. Moor administered chlorpromazine and waited to see the effect. A nurse arrived and she thought that Mr. Liddell might be in a coma, but that was not confirmed by any rigorous tests. In any event, Mr. Liddell was breathing in a manner characteristic of one close to death. The nurse left, intending to return. Dr. Moor waited with his patient, who made more retching noises. By this time the syringe driver had run out. Believing Mr. Liddell was now very close to death, Dr. Moor decided not to renew the diamorphine in the driver but gave an injection of diamorphine and chlorpromazine. His stated purpose was to ensure that the patient suffered no break-through pain. He told the relatives that Mr. Liddell had not long to live, and within about twenty minutes Mr. Liddell was dead.

Soon thereafter national newspapers reported about another doctor, who claimed to have helped patients die by means of large doses of diamorphine and also to have assisted suicide. A local journalist sought Dr. Moor's views on this, and he responded that he supported the other doctor's stance, though not on assisted suicides. That journalist reported that Dr. Moor had said that he had given many of his patients large overdoses of diamorphine to help them die a pain-free death. Mr. Liddell's case was not mentioned by name but it was referred to, and later Dr. Moor repeated his views on television, once again stressing that his actions were in the context of relieving pain. All this attracted considerable media attention; one tabloid newspaper branded Dr. Moor "Britain's greatest serial killer" and referred to him as "Doctor Death" (although there are as many differences from as similarities to Dr. Kevorkian). Inevitably, the Regional Health Authority became involved and sought a detailed account of Dr. Moor's treatment of Mr. Liddell. Frightened by the adverse publicity and the interpretations put upon his conduct, Dr. Moor neglected to mention the final injection which he had administered after the syringe driver had run dry. Similarly, in a prepared statement for the police, Dr. Moor again did not mention the final injection, although he corrected that statement some months later.

The evidence of the Crown toxicologists was that samples of Mr. Liddell's blood revealed postmortem levels indicative of an in-life injection of diamorphine up to six times greater than Dr. Moor admitted even in his final, corrected, statement. Fortunately for Dr. Moor, that damning evidence did not survive defense challenge as seriously unreliable. The trial judge directed the jurors not to rely on the Crown witnesses' evidence as to the amount of morphine which had been administered in life. This ruling significantly weakened the prosecution case, which proceeded on the basis that Dr. Moor had administered no more diamorphine than he admitted to, that is, 30 mg in the syringe driver and the additional final injection of 60 mg.

The Crown pathologist stated that Mr. Liddell was not terminally ill from cancer or any other cause, and that there was nothing physical found at postmortem which could have caused him serious physical pain. Defense experts agreed that Mr. Liddell was not terminally ill from cancer, but argued that the cancer which had been left could have been responsible for his acute pain. In addition, defense experts stated that Mr. Liddell had a serious heart condition which had been missed by the hospital and by the Crown pathologist, but which might have caused death at any moment from arrhythmia, and that this simply could not be ruled out as the cause of death. This heart condition was almost certainly responsible for Mr. Liddell's very sick, indeed terminal, appearance to eyewitnesses, including experienced nurses. In light of this defense evidence, together with the discrepancy between the Crown pathologist's finding of reasonable health and the eyewitnesses' account of Mr. Liddell's acute condition, the trial judge directed the jury not to rely on the Crown pathologist's evidence. This ruling further weakened the prosecution case. Although the prosecution sought to counter the suggestion that the heart condition was the cause of death by inviting the judge to leave the question of attempted murder to the jury, the judge declined to do so, although this had been allowed in other cases (7). That, too, was not helpful to the prosecution. Finally, it might be added that in English law the question would not ordinarily be whether or not objectively the patient was terminally ill, but whether or not the doctor subjectively believed this to be so. Accordingly, the prosecution did not seek to dispute Dr. Moor's assertion that he believed Mr. Liddell to be terminally ill and *in extremis.*

Shorn of any evidence that Mr. Liddell had received a massive overdose and that, objectively, he was neither in pain nor close to death, the remaining prosecution case did not amount to much, other than Dr. Moor's statements to the press, the untruths which he had told to the Regional Health Authority and to the police, his administration of the final dose, and some answers given to the judge, which come close to an admission of intent to kill.

Judge: You said in evidence that when you gave the final injection you intended to put Mr. Liddell to sleep. Did you think he would wake from that sleep?

Dr. Moor: No.

Judge: Death was therefore virtually certain?

Dr. Moor: Highly probable.

Judge: If he had wakened, would you have given a further similar injection and put him to sleep again?

Dr. Moor: Yes.

Judge: If he was sleeping he would not have been eating or drinking?

Dr. Moor: No.

Judge: And death would have been inevitable?

Dr. Moor: Yes.

Judge: But you only did this in the belief he was *in extremis*?

Dr. Moor: Yes.

Although substantially weakened by the judge's several rulings, the prosecution still had a tolerably strong case, because in order to convict anyone of murder, the prosecution had to prove beyond reasonable doubt only that the accused caused the death of the victim and that the accused did so with intent to cause death or grievous bodily harm (8). Beyond that, the prosecution had to negate any applicable defense. There are only three routes by which an accused can escape conviction in a murder case: one can cast sufficient doubt on causation, effectively question intention, or deploy an applicable defense.

Causation

Murder is an archetypal "result" crime: the accused must therefore actually cause the prohibited outcome. Juries are frequently told that this is a matter of common sense. Indeed as the trial judge, Patrick (later Lord) Devlin put it in his seminal direction in *Adams* (9):

> 'Cause' means nothing philosophical or technical or scientific. It means what you twelve men and women sitting as a jury would regard in a commonsense way as the cause. Manifestly there must be cases in hospitals that are going on day after day in which what a doctor does by way of giving certain treatment prolongs or shortens life by hours or even longer. The doctor who decides to administer or not to administer a drug is not, of course, thinking in terms of hours or minutes of life. He could not do his job properly if he were. If, for example, because a doctor had done something or has omitted to do something, death occurs at eleven o'clock instead of twelve o'clock, or even Monday instead of Tuesday, no people of common sense would say 'Oh, the doctor caused her death.' They would say

> that the cause of death was the illness or the injury, or whatever it was, which brought her into the hospital, and the proper medical treatment that is administered and that has an incidental effect on determining the exact moment of death is not the cause of death in any sensible use of the term.

Although this is wholly consistent with the general common law approach that normal medical treatment, even if inept and ineffective, does not break the causal chain from the original injury to the resultant death (10), it has the obvious defect of fudging questions of fact and questions of value, in that there is an implicit invitation to the jury to deploy the notion of "cause" functionally and morally for the attribution of responsibility and guilt and not analytically or scientifically as a finding of fact (11).

The point of departure in any discussion of causation and murder in the criminal law of England and Wales, especially in the context of medical treatment, is the trial of Dr. John Bodkin Adams. In 1956, Dr. Adams was arrested and charged with the murder of Mrs. Morrell, an 81-year-old patient who had died six years earlier. At the committal stage, evidence was shown that Dr. Adams had prescribed and administered such large doses of drugs, including morphine, that he must have known they would cause death. Even if the use of such drugs in quite large doses might be medically justified in cases where the patient was in severe pain, or restless, or otherwise *in extremis,* the prosecution claimed that Mrs. Morrell was not in any such condition. At the trial, the Crown provided new evidence that Dr. Adams was a beneficiary under Mrs. Morrell's will and knew that he was, but he had falsely affirmed in his cremation certificate that he was not a beneficiary.

A Crown medical expert testified that in his opinion the dosages of morphine given to the deceased shortly prior to her death must have been intended to kill her. Another Crown medical expert said the deceased could not have survived the quantity of drugs prescribed by Dr. Adams in the last few days of her life, although under cross-examination he conceded that he could not rule out the possibility that death was the result of natural causes, for example, a further cerebral hemorrhage. These Crown experts opposed the use of narcotic drugs for patients in Mrs. Morrell's condition. However, a defense medical expert did not condemn the use of such narcotics in such cases. His opinion was that death was not caused by morphine, and he did not regard the doses as excessive. Indeed, he went so far as to conclude that the dosage contributed neither directly nor indirectly to Mrs. Morrell's death. Helpful as this testimony undoubtedly was to the defense, other highly significant evidence was introduced by the defense at the trial. First, by introducing the notes made by nurses attending Mrs. Morrell at the time of her last illness, the defense effectively demonstrated that their testimony was unreliable to such a degree that the trial judge told the jury that two of the nurses "had lied in giving their testimony." Secondly, by introducing hospital records, the defense demonstrated that a different doctor had considered it right and proper to prescribe morphine for Mrs. Morrell before she was a patient of Dr. Adams.

The trial judge pointed out anomalies in the Crown case, criticized the evidence of motive, and questioned the suggestion that Dr. Adams sought to inherit Mrs. Morrell's estate. The direction to the jury included the following significant passages:

> Murder is an act or series of acts done by the prisoner which were intended to kill and did in fact kill the dead woman. It does not matter for this purpose that her death was inevitable and her days were numbered. If her life was cut short by weeks or months, it is just as much murder as if it was cut short by years.
>
> We have heard a good deal of discussion ... about the circumstances in which doctors might be justified in administering drugs which would shorten life. Cases of severe pain have been suggested and generally approved by the witnesses ... and also there have been suggested cases of helpless misery. It is my duty to tell you that the law knows of no special defense of this character. But that does not mean that a doctor who is aiding the sick and dying has to calculate in minutes or even hours, and perhaps not in days or weeks, the effect on a patient's life of the medicines which he administers or else be in peril of a charge of murder. If the first purpose of medicine, the restoration of health, can no longer be achieved, there is still much for a doctor to do, and he is

> entitled to [do] all that is proper and necessary to relieve pain and suffering even if measures he takes may incidentally shorten life.
>
> That is not because there is any special defense for medical men; it is not because doctors are put into any different category from other citizens for this purpose. The law is the same for all and what I have said rests simply upon this, which is part of the definition of murder that I gave you: no act is murder which does not cause death....
>
> But it remains the fact, members of the jury, and it remains the law, that no doctor, nor any man, no more in the case of the dying than the healthy, has the right to deliberately cut the thread of life ... [but if] the treatment that was given by Dr Adams was treatment that was designed to promote comfort and if it be the right and proper treatment in the case, the fact — if it be the fact — that incidentally it shortens her life does not give any grounds for convicting him of murder.
>
> It was a pity perhaps that the word 'justified' was ever brought into it [the case]. 'Justified' suggests to the lawyer some legal justification and it suggests to you when we are talking of matters of life and death some moral justification. There is no legal justification and there is no moral justification that you have to consider in this case. The word 'justified,' as I understand it, was used in a purely medical sense, in this way. If a doctor is going to prescribe the course of drugs that was prescribed in this case, we have heard the sort of dangers that may result: the patient may become semi-comatose; the effect on the patient who is semi-comatose may be that there are complications — pulmonary congestion and so forth — and it may lead to death, and therefore the doctor who is going to prescribe this course of treatment has to consider that, and he has to ask himself whether he is justified in a medical way in running that risk, there being in the case of a woman who is dying, always, I suppose, the risk to run that the treatment may not be the right one. And 'justified,' as I understand it, in the medical evidence is used purely in that way.

The jury acquitted Dr. Adams after 42 minutes' deliberation. The Attorney General, who prosecuted the case, entered a *nolle prosequi* in respect of a second indictment against Dr. Adams, for the murder of a Mrs. Hullett, and Dr. Adams was discharged.

Intention

With respect to the question of intent, the basic idea is that the medication is administered to kill the pain, not the patient. In Dr. Moor's case the judge instructed the jury, "Has the prosecution satisfied you so that you are sure that Dr. Moor's purpose in giving the intramuscular injection was not to give treatment which he believed in the circumstances (as he understood them) to be proper treatment to relieve George Liddell's pain and suffering?" If the answer is "No," the jury should acquit, but if the answer is "Yes," the jury is to resolve the final question: "Has the prosecution satisfied you so that you are sure that the defendant when he gave the intramuscular injection intended to kill George Liddell"? If the answer is "No," the jury should acquit, but if "Yes" then the jury should convict.

These questions only arise where the jury has already determined that the doctor has caused death, so that the only question which then remains is one of intention. What is sometimes called direct intention involves purpose, objective, want, or desire. The directly intended consequence is one which the agent wants or desires, and would account the project a failure if that consequence did not occur (12). What is sometimes called oblique or indirect intention refers to consequences which are not desired or wanted and which are not part of the agent's purposes or objectives but which the agent foresees as probable, highly probable, or virtually certain to occur. There are two closely related but distinct questions about this: (a) is such a state of mind properly referred to as "intention" at all, when it is obviously not intention but foresight? and (b) should agents be held legally or morally responsible both for directly intended consequences and for consequences not directly intended but foreseen as probable, highly probable, or virtually certain?

The criminal law of England and Wales has vacillated on the first of these questions but has settled on a clear distinction between intention and foresight, while holding that a jury is entitled to find a defendant intended a consequence if it was actually foreseen as virtually certain to occur (13). It therefore follows that a jury is entitled to find that a doctor whose direct intention was to kill the pain, not the patient, also intended that patient's death if the doctor foresaw it as probable in a sufficiently high degree. But being entitled is not the same as being bound, and it is therefore also open to a jury not to find intention even in the presence of foresight of death as a virtual certainty (14). This means that when a jury is persuaded that a doctor acted to kill pain, not the patient, no matter how likely death was to result, and is also persuaded that the means used fall within the range of proper treatment to relieve pain, it is entitled not to find the requisite intention and can properly acquit on a charge of murder for want of proof of the requisite intention. But useful though this obviously is to lawyers defending doctors on such charges, it is not uniquely a "doctor's defense," because it is in principle available to a conscientious jury in any case where an agent knowingly brought about death, directly intending some beneficial result. For example, where a member of a bomb disposal team drives a car booby-trapped with a time-bomb away from a very crowded location at high speed in the few minutes before timed detonation, at and over innocent pedestrians. The principle of double effect is plainly not limited to cases involving medical treatment of the terminally ill.

Criminal law in England and Wales holds that, in general, agents should be held legally responsible both for directly intended consequences and for consequences not directly intended but foreseen as probable, highly probable, or virtually certain. The principle of double effect, however, asserts that there is a morally relevant distinction between directly intended consequences and foreseen but unintended consequences. Thus, under this principle it is sometimes permissible foreseeably to bring about a result which it is never permissible to intend, but the principle requires that the bad effect be unintended, not disproportionate to the intended good effect, and unavoidable (15). Given that for some "... the patient's good does not include death" (16), it is perhaps counterintuitive that death can ever be proportionate to the intended good effect, even where the pain and hopelessness of the patient is extreme.

If a doctor injects a severely ill patient with a powerful painkiller in the certain knowledge that the drug will cause death within a matter of minutes, it is at best a transparent legal fiction to say that he or she intended to relieve the pain but did not intend to kill. It would be at least as true to say that the doctor intentionally killed the patient in order to prevent further suffering (17). But two distinguishable cases are conflated here, and their untangling reveals that the principle of double effect is also arbitrary. Are doctors morally and perhaps legally prohibited from acting in cases where there appears to be the greatest need to relieve pain? It is an unhappy conclusion that the point comes where the doctor must cease treatment of pain on liability for murder. Of course, distinguishing the two categories of case hypothesized above will not be at all easy in practice, and there is an obvious temptation to interpret cases of the second type as falling into the first category and therefore apt cases for continued treatment.

There are cases in which there is sufficient evidence of intention but genuine doubt as to causation. For example, the deceased may have died from causes other than the medication, such as the heart condition suggested by the defense in Dr. Moor's case. In such cases the common law court may proceed on the basis of attempted murder (7). This is because purpose is not required for criminal attempt: "The bounds are presently set requiring proof of specific intent, a decision to bring about, in so far as it lies within the accused's power, the commission of the offense which it is alleged the accused attempted to commit, no matter whether the accused desired that consequence of his act or not" (18). This understanding of the nature of "intention" required for criminal attempt has seemed to some an arbitrary and unprincipled "extension" (19) and it is perhaps unpersuasive to treat one who foresees an undesired or unwanted outcome as virtually certain, as "attempting" to bring about that outcome. If, however, "purpose" were to be a requirement for criminal attempt, then it would be very difficult to substitute a charge of attempted murder for one of murder in cases of the type under consideration.

Dr. Nigel Leigh Cox, a consultant rheumatologist at the Royal Hampshire County Hospital, was indicted on a charge of attempted murder of his patient Lillian Boyes, on August 16, 1991. The patient was dying and in great pain. A short time before her death the accused intravenously administered to her an undiluted injection of two ampules of potassium chloride. The prosecution provided evidence that, injected in that manner and that quantity, the drug had no therapeutic property and that the accused's intention in so administering it was to end the life of his patient. The defense argued that the primary purpose had been to relieve the pain of the dying patient and that therefore there was no intention to kill Lillian Boyes. The prosecution conceded that, with regard to Mrs. Boyes's condition on the morning of the fatal day, they could not exclude the possibility that, in fact, she died of natural causes between the actual injection of potassium chloride and her death. For that reason the charge was not one of murder but of attempted murder. It is possible that this did a disservice to the accused, because it is easier even in so "sad and testing" a case for a jury to convict of the attempt rather than the full crime, knowing that there is no mandatory sentence for the former.

In the course of his direction to the jury, the trial judge paid tribute both to the "indomitable" and "resourceful" character of the deceased and the "exemplary character" of the accused. He mentioned the very special regard in which Dr. Cox was held and the very close bond which had developed between doctor and patient over 13 years. The judge explained that there is an "absolute prohibition on a doctor purposely taking life" and that Dr. Cox would be guilty "if he injected her with potassium chloride for the primary purpose of killing her, or hastening her death." The judge also stressed that "if a doctor genuinely believes that a certain course is beneficial to his patient either therapeutically or analgesically, then even though he recognizes that that course carries with it a risk to life, he is fully entitled, nonetheless, to pursue it. If in these circumstances the patient dies, nobody could possibly suggest that in that situation the doctor was guilty of murder or attempted murder." Dr. Cox's duty to do all that he could for his patient was recognized, but "what can never be lawful is the use of drugs with the primary purpose of hastening death." Further, "it matters not by how much or by how little her death was hastened or intended to be hastened." There was evidence that Mrs. Boyes was at best hours or possibly only minutes away from death when she received the injection. Even so, "no doctor can lawfully take any steps deliberately to hasten that death by however short a period of time."

It is relevant to note that Mrs. Boyes had "signed her own death warrant" on August 11 by declining (as she was wholly entitled to) any further active medical treatment and specifying that she should receive only painkillers. The following day Dr. Cox reported to Mrs. Boyes's sons that she had asked to be given something to hasten death and that he had told her that he could not do that, but that he would certainly make her comfortable. By this time Mrs. Boyes was in great pain and the cessation of her steroid treatment must have exacerbated this pain. She was receiving diamorphine at the rate of 60 mg per hour (which rather puts Dr. Moor's prescription and injection into perspective), having started at less than 1 mg. Dr. Cox was very distressed by Mrs. Boyes's suffering. In that state he injected neat potassium chloride. It was common ground at the trial that in such a case this drug had no curative or analgesic properties, or clinical use, and, as "any doctor would know," injected neat, one ampule, let alone two, would certainly kill. In addition, there was expert testimony that since this drug was not a therapeutic option to alleviate pain from a purely physiological perspective, there could be no other purpose in its administration than the hastening of death. But that testimony also acknowledged that the probable effect of the injection was indeed to alleviate suffering only by bringing her life to an end. What we have here, therefore, is a case of death as a means of alleviating pain, rather than an instance of death as an effect only incidental to the alleviation of pain. There was indeed testimony that, with regard to the patient's uniquely grave condition, there was no other way of controlling the pain, and although the deliberate shortening of life to alleviate pain is "not proper," the expert hoped that if he was confronted with such circumstances he "would have the courage to do what Dr Cox did." This confusion is understandable, given the state of the law, but it is intriguing that what appears to be morally proper is not perceived as medically proper.

Although Dr. Cox did not testify on his own behalf in court, defense counsel argued passionately for his client. He suggested that, faced with a terminally ill patient in severe pain, there is an air of unreality, even absurdity, in asking what the doctor's primary purpose was, because the line to be drawn between alleviating pain by means which incidentally cause death and causing death in order to alleviate pain for however short a period is so fine and subtle as to be incapable of sensible application by any doctor confronted with this particular situation. As Counsel put it, "Five minutes of peace is not very much but it was all Dr. Cox could give, and he gave it." Counsel also elaborated on the use by Dr. Cox of other quite slow acting drugs and on his openness in recording the use of the potassium. What Counsel sought to persuade the jury was that all this was a way, albeit unorthodox, of relieving pain and suffering. Notwithstanding this passionate plea, the jury convicted Dr. Cox, who was sentenced to one year's imprisonment, which was then suspended. However, there were limits to the judge's compassion; whereas he acknowledged that what could not be excused could be explained, he responded to Counsel's plea for an unconditional discharge in view of the exceptional facts, "that deliberate conduct by a doctor aimed at bringing about the death of a patient required, as a matter of principle, to be marked by a term of imprisonment" (20). That plainly entails criminal liability and the sanction of imprisonment in all cases of mercy killing: "Since euthanasia will relieve the patient's suffering only by killing the patient, the physician cannot reasonably intend that the patient not die" (3).

Under the predictable heading "Hard cases make bad law," the *New Law Journal* (21) editorialized on a conviction which on the facts was "probably inevitable" but "we are not clear how the conviction of Dr Cox has helped anyone." Given that it genuinely could not be said that the injection killed the patient, because she was so near to death that she might in any event have died from natural causes, the editor wanted to know how it could be in the public interest to prosecute. This alone is enough to call into question the peculiar "extension" in the meaning of intention which legitimates charges of criminal attempt in such circumstances. Of course, "absolute horror" would have been rightly expressed had a mandatory life sentence been visited on Dr. Cox. As to what the General Medical Council should do about the matter, the editor helpfully suggested "that a suspension of 24 hours would be more than adequate," noting that "an expert medical witness at the subsequent General Medical Council hearing said that Dr. Cox's mistake was to give potassium chloride; [whereas] a large dose of sedative causing [Mrs. Boyes] to lapse into a coma would have fallen on the right side of the law" (4). Apparently Dr. Cox could then have credibly said or plausibly claimed that his purpose was to alleviate pain and not to cause death, although the effect on the patient would have been precisely the same in all material respects and it has seemed to some that "terminal sedation is a method of death that is ethically inferior to assisted suicide" (3). This illustrates the moral limits of the principle of double effect and the shortcomings of the criminal law of England and Wales as it is currently understood. Regrettably, it requires hypocrisy, evasion, and untruth within what is a relationship of trust. And, what is far worse, it results in an extended, miserable and undignified death.

The reasoning and outcome of Dr. Cox's case compares unfavorably with the little known and rarely discussed case of Dr. Thomas Lodwig (22), a former senior house officer at Battle Hospital, Reading. In 1989 Dr. Lodwig was committed for trial by the Reading magistrates, charged with the murder of Roy Spratley, a 48-year-old male patient who was in the terminal stages of incurable cancer of the pancreas, which had been diagnosed in June 1987. Although he had been given six months to live, he died on September 29, 1988. In the days before his death the patient was no longer lucid and suffered terrible and uncontrollable pain. His family pressed Dr. Lodwig to do something further to relieve it. Shortly before Mr. Spratley died, Dr. Lodwig asked a nurse to fetch an ampule of potassium chloride and some lignocaine, which he infused. The patient died peacefully a few minutes later, although the precise time of death was not recorded; nor was the administration of potassium chloride and lignocaine (unlike what happened in Dr. Cox's case). Following concerns expressed by nurses and administrators, the police treated the death as suspicious, and a forensic pathologist retained by the prosecution, who performed a postmortem on Mr. Spratley, entered the cause of death as acute potassium poisoning.

For many months before his death (which was expected within hours, days or weeks), Mr. Spratley had been receiving regular injections of heroin in increasing dosages for the purposes of pain relief. This was no longer effective in the days before his death, notwithstanding that the postmortem examinations revealed morphine levels of 5.4 mg/L, said by the toxicologist to be the highest levels that he had seen. Accordingly, Mr. Spratley could have died from heroin at any time, or from his tumor, and in addition he had significant narrowing of the coronary arteries. On Dr. Lodwig's behalf, it was said that it was his intention to kill the pain and not the patient. In addition it was reported that experiments had been conducted using potassium chloride with painkillers to accelerate their painkilling effect, and the results from animal and clinical trials had been "encouraging," but as yet none of these have been published. There is a further suggestion that this research may have been conducted at St Bartholomew's Hospital, London, where Dr. Lodwig had finished his training about three years before he was charged (22). On March 15, 1990, Dr. Lodwig was acquitted by direction at the Old Bailey after the prosecution decided to offer no evidence at his trial and admitted that it was no longer convinced that Mr. Spratley had died from a potassium overdose.

It is very troubling that these two very similar cases had such different outcomes, and one wonders why the prosecution pressed on relentlessly with a count of attempted murder, in Dr. Cox's case but not in Dr. Lodwig's, and why the potential of potassium chloride to facilitate the operation of painkillers, which might have gone some way towards blunting some of the prosecution's sharper points, was not part of the defense in the later case. Perhaps the research was never written up and published, and perhaps it did not amount to anything very impressive at the end of the day. But it remains disturbing that the criminal justice system could exhibit two such different outcomes on what appear to be broadly similar facts. Unfortunately, much seems to turn upon prosecutorial discretion and the predilections of the trial judge. Above all, the law is uncertain and incapable of giving adequate guidance.

It is one thing to agree with the BMA's Euthanasia Report that "Any doctor, compelled by conscience to intervene to end a person's life, will do so prepared to face the closest scrutiny of this action that the law might wish to make" (22) and quite another to conclude that this scrutiny is arbitrary and random, rather than principled and transparent. A distinguished commentator on Dr. Moor's case recalled that "Sybille Bedford called her account of the trial of Dr. Bodkin Adams 'The Best We Can Do'" and added, "Perhaps this is still the best we can do" (4), but surely this is not the best we can do almost half a century on from Dr. Adams's case. In Britain we need a euthanasia and terminal care act and we need it now. However, a House of Lords Select Committee on Medical Ethics, which reported in 1994, was against any change in the law to permit euthanasia, because this would "weaken society's prohibition of intentional killing."

Professional Ethics

If there is a doctor's defense, it is a defense based on professional ethics and not on minimal causation or the doctrine of double effect. I argue that a virtue ethics (23) approach is more inclusive and less doctrinaire than the principle of double effect. So any commonsense distinction between accelerating and causing will not prove helpful beyond such cases where the medical treatment so slightly accelerates death as to be virtually no cause. However, because a doctor has a professional duty to relieve a patient's suffering, "it is permissible for him, when the patient is doomed to die shortly, to administer painkilling drugs with his consent even if they shorten life ... it does not follow that it would be permissible, as opposed to understandable, for someone without such a duty to do the same" (24). But this has "abandoned the lack-of-causation defense and to have embraced a special doctor's defense instead ... we cannot distinguish between a doctor and a layman doing the same act on grounds of causation, but only on the ground that what is permissible for the one is not permissible for the other" (4).

All moral agents have duties, and it might plausibly be suggested that there is moral virtue in anyone reducing human pain and suffering, but it is also plausible that this is a virtue specific to doctors in a high degree: "Our society broadly recognizes the necessity and appropriateness of allowing doctors to do what others are forbidden from doing" (25). For example, doctors are permitted to look at and even touch our naked bodies in ways which would be morally impermissible for others.

Some are unhappy about distinguishing between doctors and non-doctors, and think that it is unacceptable that there should be different judicial directions (on *mens rea*) in criminal trials "depending on the identity of the defendant" (5). In response, it should be noted, first, that it is not so much the "identity" but rather the professional status and role of the defendant which is relevant. However, if one recognizes that doctors have ethical duties which differentiate them from non-doctors, one may seek to have these differences recognized by the criminal law. This is controversial, in that what ethical duties are implicit in the doctor's role is itself contested. One distinguished view of the ethics of medical practice is that "physicians, under no circumstances, should be parties in assisting patients in ending their lives" (16). Another "conception of physician duty [is that] under certain circumstances physicians have a moral responsibility to assist a patient in hastening death" (25).

In my own view there can be no general ethical duty of doctors to assist suicide as that is conventionally understood; quite the reverse. Doctors, one might think above all others, ordinarily should discourage suicide and even heroically strive to save the life of an attempted suicide (25), and in my experience they do, and rightly so. In similar vein the judge in Dr. Cox's case observed, that "patients, however gravely ill, often confound the doctor's prognosis and make a recovery that defies all expert expectations. That is, no doubt, one of many reasons that leads [sic] to the absolute prohibition on a doctor purposefully taking life, as opposed to saving it" (26).

But I distinguish suicide in general from treatment of the terminally ill, where different moral considerations apply. Ideally, deaths occurring in the context of medical treatment of the terminally ill should be taken outside the ambit of the general criminal law and dealt with on a separate statutory basis. And any statute should take account of the moral mission of the medical professions, so that where motivated by proper medical concern to relieve suffering and to respect patient autonomy, a death would no more result in a charge of murder than surgery would provoke a charge of unlawful wounding (25). And, failing legislation, common law courts should develop the law so as to accommodate professional ethics, mindful of the distinction between doctors and non-doctors.

The distinction between doctors and non-doctors is warranted, if at all, only by reference to the special moral duties incumbent on doctors by virtue of their being doctors, and that is a professional ethics argument which invokes virtue ethics and does not hold to the artificial distinction between knowing and intending. In arguing, as I think persuasively, that there is "no moral difference between killing and letting die" (25), Rosamond Rhodes deploys what I shall call "the transitivity argument," moving from the conventional moral acceptability of "letting die" to the proposed moral acceptability of "causing (or hastening) death." In this paper I deploy a similar transitivity argument, moving from the conventional moral (and legal) acceptability of prescribing painkilling drugs which incidentally hasten death to the proposed moral (and legal) acceptability of causing (or hastening) death as a means of or for the purpose of alleviating pain. On the basis that the law should aspire to be moral in general and should, in particular, respect professional ethics, the argument for legal acceptability is contingent on winning the moral argument, both with doctors and with the public.

The conclusion that a doctor may prescribe and administer painkilling drugs even if that has the incidental effect of causing death, without being exposed to a murder charge, flows from the doctor's ethical duty to alleviate pain and suffering. It is not a defense based on the absence of causation or of intention. It is an exception or override based upon the doctor's moral mission. There is widespread reluctance to recognize that the doctor's duty is the true basis of the doctor's defense, because, as currently recognized by the criminal law of England and Wales, the doctor's defense is an unhappily truncated affair and full recognition would call for fuller implementation of the doctor's defense. Given that a doctor (such as Dr. Moor) can (morally and legally) prescribe death-accelerating drugs where death is incidental and foreseen but not intended, nor a causally necessary means to alleviating pain, why cannot a doctor (such as Dr. Cox) simply prescribe (morally or legally) the same or different drugs where death is intended as the only means to alleviate human suffering? The doctrine of double effect and the "bishop's argument" that "there is a proper and fundamental ethical distinction which cannot be ignored between that which is intended and that which is foreseen but unintended" (27) prevents that extension. But the suggestion that had Dr. Cox only used a sedative, there would have been nothing wrong simply misses the moral mission of medicine in the presence of someone like Lillian Boyes: "there are some dying patients who experience suffering that is intolerable and that cannot be relieved by traditional medical care" (3).

It is probable that some, perhaps many, doctors and other health care workers placed in Dr. Cox's position would have acted in a similar way: "surely many a nurse has engaged both in involuntary as well as voluntary euthanasia, and one can be sure that many would readily volunteer" (16), although it may be that this author meant to distinguish what is ethically proper for *doctors* from that which is ethically permissible for other health care workers, including *nurses*. The Voluntary Euthanasia Society, albeit hardly an impartial observer, believes that in the United Kingdom up to 100,000 patients a year are quietly helped to die (28). Dr. Moor's prosecution was seen by many as an abuse of the criminal law, and even those who welcomed the prosecution were disappointed, even "appalled" by what they saw as a green light to "backdoor euthanasia," which is said by some reporters to be favored by 60% of doctors (28). Although Dr. Moor's acquittal was hailed as a victory for euthanasia, plainly it was not, and Dr. Moor himself certainly did not see it as such. And it was not such a victory precisely because it maintained the distinction, however philosophically suspect, that there is a moral and a legal difference between prescribing painkilling drugs which may incidentally hasten death, and causing death as a means to alleviating pain. On the other hand, had Dr. Cox been acquitted, one might have been able to hail that as a victory for euthanasia. The reduction of the charge to attempted murder, the modest penalty, the condemnation of the prosecution, and the conviction all suggest that even 10 years ago the tide seemed to be running for euthanasia.

I want to revert, briefly, to some ideas developed in the context of medical ethics and confidentiality, and in particular to the concept of a "recourse role" (29). By a recourse role I mean a role than enables the agent to take action in situations where the role's prescribed ends conflict among themselves or with its prescribed means. Thus, "alleviating pain" may sometimes conflict with "preserving life." Recourse roles provide for such situations by establishing conditions under which the agent may be justified in undertaking actions that depart from the primary role requirements. Recourse roles extend a liberty in handling role obligations. This imposes a moral burden, because the choice between conflicting obligations is left to the agent as a moral responsibility of the role. I have argued that "the role of the health care worker may be a recourse role, in that it is embedded in the legal system in a particular way which allows good faith judgment in the resolution of the dilemmas of the role even where the resolution may appear to conflict with primary legal rules. Simply because answers cannot be prepared in advance, decisions have to be made and respected in the context of the role. In so far as the legal system respects, or at least reveals a tendency to respect, these decisions, they are, at least in part, both role defining and law-making, or law-shaping" (29). However, this is normally not a solitary but a collective venture: "decisions to cooperate with hastening patients' deaths are discussed in the semipublic arena of team decision-making and unit-conferences, thereby giving physicians the opportunity to reexamine cases, to justify their decisions to their peers, to raise additional considerations, and to voice objections. This ongoing practice has allowed doctors and their institutions to accumulate substantial experience in managing life-ending decisions. And because of the generally satisfactory results, our society has come to trust doctors to cooperate with patient decisions" (25). Doctors who, like Dr. Cox and perhaps Dr. Moor, make the hard decisions at the limits of recognized proper practice are moral pioneers whose risk-taking may make it easier for other doctors to honor their professional duties without exposure to criminal prosecution.

On the view of medical ethics which I favor, doctors "have a greater obligation than others to provide help in hastening death" (25). I agree with Phillipa Foot that, for some, life is no longer a basic good but has become an evil, that there is no conceptual connection between "life" and "good," and that "to save or prolong a man's life is not always to do him a service" (30). I also agree with Rosamond Rhodes that "a doctor's commitment to acting for patients' good creates a clear obligation to help a patient avoid an agonizing, protracted death" (25). Quoting Dr. Smalhout, an anesthetist then practicing in Utrecht and translated from the Dutch *Een Monument van onmacht en lafheid* (A Monument to Incompetence and Cowardice), published in the general press (*NRC Handelsblad*) on January15, 1990, Diana Brahams reports that such a "death is dreadful to watch. The skin and the muscosa dry out; the blood thickens; the kidneys no longer produce urine and gradually die. The eyes become damaged for the lack of tears; the mouth is infested by fungal infections because the natural cleaning by saliva is lost. The body is gradually poisoned by the breakdown of products which can no longer be excreted. In the airways crusts of dried mucus develop which makes breathing steadily more difficult and so the unconscious patient fades away under the eyes of doctors, nurses and family. It can well take ten days or more before death arrives and in dying the patient becomes a monument to medical and judicial cowardice and hypocrisy" (22). Is this really "the best we can do"? Or is a good death a moral and legal option?

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Is HIV Infection a Risk Factor for Complications of Surgery?

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Abstract

Background: The literature is inconsistent as to whether HIV-infected patients have higher rates of surgical complication than do HIV-uninfected patients. This inconsistency reflects the failure to control for confounding variables in many of the previous studies.

Methods: A retrospective cohort study of records of HIV-infected individuals who underwent surgical procedures between 1990 and 1995 was matched with the records of HIV-uninfected control patients. We performed a logistic regression analysis to determine the independent effects of HIV infection and other potential risk factors for surgical complications.

Results: The crude rates of death and infectious and hematologic complications were higher among HIV-infected patients than among uninfected patients. Although the crude risk of having any complication was higher among the HIV-infected (odds ratio [OR]=2.47, $p=0.015$), the adjusted risk was not (OR=0.72 [$p<0.613$]). Variables significantly associated with complications were American Society of Anesthesiology (ASA) risk class (OR=2.7), age (OR=1.06 per year), and weight (OR=0.96 per kg).

Conclusions: HIV sero-status was not found to be an independent risk factor for complications of surgery. The most important risk factor for complication of surgery in HIV-infected patients is ASA risk class.

Key Words: AIDS, HIV, surgery, complication.

Introduction

DO HUMAN IMMUNODEFICIENCY VIRUS (HIV)-infected persons have higher surgical complication rates than do uninfected persons? The literature is remarkably inconsistent on this subject, with results of surgery reported as unacceptably poor (1–5) or remarkably favorable (6–11). A recent review found that the surgical literature consists mostly of descriptive, retrospective case series, with wide variability of the reported patient populations, surgical procedures, and methods for collecting and categorizing information on complications (12). Few studies used analytical methods to minimize confounding the comparison of groups with risk factors known to be associated with post-operative complications such as emergency procedures, malnutrition, contaminated wounds, uncontrolled diabetes and neutropenia. Of 114 reports of the outcome of surgery in HIV-infected and uninfected persons, only 10 studies matched groups by one or more variables, and only two of these found significant differences in complication rates (13, 14). We attempted to correct for these weaknesses in this retrospective cohort study by including relevant variables in the analysis. The purpose of the study was to determine if HIV infection is an independent risk factor for complications of surgery.

Methods

We reviewed the records of all HIV-infected patients who underwent a surgical procedure at Mount Sinai Medical Center, New York, from 1990 to 1995. Patients were identified through the hospital's discharge database and were included as cases if they had acquired immunodeficiency syndrome (AIDS) as defined by Centers for Disease Control and Prevention criteria (15) or if they had HIV infection, and a CD4

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lymphocyte count had been performed within four months of surgery. Each HIV-infected patient was matched with two control patients for three variables: surgical procedure, age within 6 years and year of procedure within 5 years. Control patients were identified through the hospital's discharge database as having had the same procedure as HIV-infected cases, but not coded as having HIV infection or AIDS. When more than two control patients were available who matched with a particular case, selections were made randomly. Control patients were excluded if they had known risk factors for HIV transmission, if they had been treated with antineoplastic chemotherapy within one year of surgery, or if they had undergone organ transplantation. Each patient treated with high-dose corticosteroids within six months of surgery was matched with two controls similarly treated. Demographic and clinical information was entered into a database that included: indication for surgery, type of surgical procedure, emergent or elective surgery, anesthetic type, presence or absence of cardiopulmonary disease, pre-procedure antibiotics, CD4 count, serum albumin level, serum creatinine level, white blood cell (WBC) count, hematocrit, prothrombin time, serum alanine transaminase (ALT) level and American Society of Anesthesiology (ASA) risk class. Chemistry and hematologic laboratory values recorded were those obtained closest to the time of surgery. ASA risk class is a global rating based upon the anesthesiologist's assessment of the physical status of the patient: class I, normal healthy patient; class II, patient with mild systemic disease; class III, patient with severe systemic disease that limits activity but is not incapacitating; class IV, patient with incapacitating illness that is a constant threat to life; and class V, moribund patient not expected to survive 24 hours with or without operation (16).

Peri-operative and post-operative events were recorded as complications if they occurred within 30 days of surgery and if they were described in the medical record as a complication or an unexpected event. An event was classified as a complication if it met one of the following criteria: (a) death; (b) re-hospitalization or return to the operating room; (c) intra-operative complication (either surgical or anesthetic); (d) clinically apparent bleeding; (e) post-operative fever lasting more than 72 hours (all cases were ultimately found to have an infectious cause); (f) clinical diagnosis of infection requiring antibiotic treatment outside of routine prophylaxis; (g) extubation delayed by more than 24 hours or re-intubation; (h) post-operative bowel obstruction or ileus requiring placement of a naso-gastric tube; or (i) other clinically significant events such as post-operative deep vein thrombosis, cardiac arrhythmia or renal failure. All of the above information was obtained by direct review of the medical records and entered onto a standardized data collection form. Approval for this study was obtained from the Mount Sinai School of Medicine Institutional Review Board (IRB).

Statistical Analysis

Hypothesis testing was carried out using logistic regression to control for year of surgical procedure, ASA risk class, emergent versus elective surgery, age, gender, hematocrit, WBC count, platelet count, serum albumin, ALT, creatinine levels and body weight. The effect of clustering of patients by surgeons and type of surgery on standard errors was accounted for by using the Huber-White robust covariance estimator (17). Cases were dropped from analysis if data for any of the variables under analysis were missing.

Results

Study Population

Of the 52 HIV-infected patients identified and 104 HIV-uninfected controls, 26 were excluded from analysis due to missing variables. This resulted in 130 patients available for analysis: 43 with HIV infection and 87 without HIV infection. The demographic and clinical characteristics of the study population are outlined in Table 1. The HIV-infected and HIV-uninfected groups were well matched for age. A greater proportion of HIV-infected patients were males, compared to the uninfected patients. Similarly, a greater proportion of HIV-infected patients were non-white, compared to the uninfected patients. The majority of HIV-infected individuals (75%) were defined as having AIDS by virtue of a CD4 count <200 cells/μL. The mean CD4 count of the HIV-infected individuals was 177 cells/μL. The mean CD4 count of HIV-infected individuals excluded from the analysis was 152 cells/μL, which is not a statistically significant difference. Furthermore, the proportion of patients with a CD4 cell count less than 200 per μL was the same for patients included in the analysis as

TABLE 1
Demographics and Clinical Variables

	HIV-infected n=43	HIV-uninfected n=87	Normal values
Male, %	74	43	
Age, mean yrs	42 ± 9	43 ± 11	
Ethnicity			
African-American, %	35	10	
Asian, %	0	6	
White, %	40	68	
Hispanic, %	23	14	
Emergent surgery	58%	30%	
CD4 count, mean cells/μL	177 ± 226	—	480–1700
CD4 count<200 cells/μL, %	75	—	
Serum albumin, g/mL	3.4 ± 0.8	4.3 ± 0.5	3.5–4.9
ALT level, U/L	71 ± 74.6	30.3 ± 27.4	1–53
Serum creatinine, mg/mL	2.1 ± 4	1.1 ± 1.1	0.5–1.3
WBC, cells/mm^3	6.6 ± 3.8	8.9 ± 4.1	5–11
Hematocrit, %	32.8 ± 8.3	39.1 ± 4.8	34–48
Platelet count, cells/mm^3	201 ± 107	282 ± 97.7	150–450
Weight, kg	65.2 ± 11.1	71.3 ± 17.4	

for those who were excluded. Analyzed and excluded patients had similar values for all variables (data not shown).

Procedures

The types of procedure performed are listed in Table 2. A majority of these procedures were major abdominal surgeries, either clean or contaminated. None of the major abdominal procedures were performed by laparoscopic surgery. The mixed category includes those patients who underwent combined procedures — most commonly abdominal and thoracic. Almost twice as many HIV-infected patients underwent procedures on an emergent basis as did patients who were not HIV-infected: 58% vs. 30%, p=0.001 (Table 1).

TABLE 2
Surgical Procedure Types

Procedure Type	HIV-infected n=43	HIV-uninfected n=87
Abdominal clean	18	38
Abdominal contaminated	7	9
Appendectomy clean	3	7
Appendectomy contaminated	4	6
Cardiothoracic	1	2
Bone	0	2
Head and neck	3	7
Mixed*	1	4
Pelvic clean	4	6
Pelvic contaminated	2	6

*Procedures involving both abdominal and thoracic cavity

Complications

Table 3 lists the types and corresponding numbers of complications that occurred in each group. Procedural complications were defined as those directly related to the procedure, such as technical complications occurring intraoperatively or bowel obstruction occurring postoperatively. Complications classified as organ dysfunction were those related to dysfunction of an organ system not directly related to the surgical procedure, such as renal failure, cardiac arrhythmia or respiratory failure. Infectious complications were the most common type of complication in each group, accounting for approximately half of all complications for both the HIV-infected and uninfected patients. Other types of complication, including death, were similarly distributed in both groups.

The crude rates of death, infectious and hematological complications were slightly higher among HIV-infected than the uninfected. The crude risk of having any complication was higher among the HIV-infected, OR=2.47 (p=0.015).

TABLE 3
Complications of Surgery

Type of Complication	HIV Status	
	Infected n=43	Uninfected n=87
Death	3	2
Hematologic	3	0
Infectious	17	13
Organ dysfunction	3	3
Procedural*	4	7
Total	30	25

*Complications related directly to the procedure

TABLE 4
Logistic Regression Analysis of Risk Factors for Complications of Surgery
Number of Observations = 130

Risk Factor	Odds Ratio	(95% C.I.)
ASA risk class**	2.70	(1.50 ± 4.84)
Emergent surgery	1.13	(0.40 ± 3.18)
Procedure year	1.12	(0.85 ± 1.46)
WBC count	1.09	(0.96 ± 1.25)
Age*	1.06	(1.01 ± 1.11)
Hematocrit	1.01	(0.93 ± 1.11)
ALT level	1.00	(0.99 ± 1.01)
Platelet count	1.00	(0.99 ± 1.00)
Gender	0.97	(0.31 ± 3.06)
Weight*	0.96	(0.93 ± 1.00)
Creatinine level	0.87	(0.75 ± 1.02)
HIV infection	0.72	(0.20 ± 2.62)
Albumin level	0.62	(0.26 ± 1.51)

Robust standard errors in parentheses. * Significant at 5% level. **Significant at 1% level. Area under ROC curve=0.80. Hosmer-Lemeshow Goodness of Fit χ^2=6.69 (p=0.57).

In the logistic regression analysis, however, the adjusted OR of having any complication and having HIV infection was 0.72 (p<0.613) (Table 4). The greatest and most statistically significant association with surgical complication was ASA risk class, OR=2.70 (p=0.001). Both age and weight were also significantly associated with the risk of complication, with ORs of 1.06 per year and 0.96 per kilogram respectively. In addition to HIV infection, other potential risk factors found not to be significantly associated with complications of surgery were emergent surgery, procedure year, WBC count, hematocrit, serum ALT level, platelet count, gender, creatinine level, and albumin level.

A sub-analysis (data not shown) separating HIV-infected patients with CD4 counts of 200/μL or greater from those with counts of less than 200 cells/μL did not show a significant difference in association with surgical complications. However, the number of HIV-infected patients with CD4 counts of 200 cells/μL or greater was low, limiting the statistical power of this analysis.

Discussion

HIV sero-status was not found to be an independent risk factor for complications of surgery in our retrospective cohort study. Although the crude risk of HIV-infected patients having any complication was 2.47 times greater than for uninfected persons, a logistic regression analysis demonstrated that controlling for known risk factors eliminates the significant difference in complication rates between infected and uninfected patients. We found the most important risk factor for complications to be ASA risk class.

The discordance between the crude and adjusted odds ratios found in our study may explain the variability in complication rates found in the literature. A review of published studies documented inconsistent complication rates among HIV-infected patients for all fields of surgery (12). The field with the narrowest range of complication rates was dental surgery, and even here the reported rates ranged from 1–20%. In the literature of major abdominal surgery, complication rates in HIV-infected patients ranged from zero to an average of 1.6 complications per patient, and mortality rates ranged from 0–60% (12).

Few published studies used analytical methods to minimize confounding for surgical complications by known risk factors (12). In a review of 114 reports describing complications in HIV-infected patients (12), only 3 reports, all cohort studies, were notable for their rigorous study designs (14, 18, 19). Only one of these studies found significantly greater complication rates in HIV-infected patients, and only for minor complications (14).

In several recent reports, surgical complication rates were found to be greater in HIV-infected patients than in uninfected patients (20–23). However, in each of the studies, the groups were matched only by age and gender, not by clinical variables or ASA risk class.

Our study matched patients by procedure type, age and year of procedure and then compared the effect of known risk factors on the complication rates between infected and uninfected patients. Nearly twice as many HIV-infected patients had emergency operations as did uninfected patients, and although not statistically significant, HIV-infected patients tended to have lower weight, serum albumin levels, platelet and WBC counts, and higher serum ALT and creatinine levels.

Our study had several important limitations. First, we studied patients who contracted HIV infection in the years before the general use of highly active antiretroviral therapy (HAART). However, current standard therapies are known to decrease the risk for bacterial infections, improve nutritional status, and increase life expectancy (24), and one might reasonably expect that patients would tolerate surgery even better in the HAART era. Second, our sample size was not great enough to determine the contribution of more than a few known risk factors for surgical complications. As a result, the study's power to rule out the contribution of each of the examined variables was relatively low. Although we found a relative risk of 0.72 for the association of HIV infection and surgical complications, the 95% confidence intervals ranged from 0.20 to 2.62. Third, the retrospective study design resulted in the exclusion of many patients because of incomplete study variables. Finally, we did not document the seronegative status of control patients. We did, however, exclude from the control group all patients with risk factors for HIV infection.

Conclusion

We found no evidence to support an independent effect of HIV infection on the risk of surgical complications. We found instead that ASA risk class, a measure of general health status and preoperative risk, most closely correlates with complication rates. HAART has resulted in sharply diminished morbidity and mortality of HIV-infected patients. Still to be determined is the effect of HAART on the risks and outcomes of surgery.

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Choriocarcinoma in a Patient with Human Immunodeficiency Virus:

Case Presentation and Review of the Literature

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Abstract

A 26-year-old woman with choriocarcinoma and acquired immunodeficiency syndrome initially presented with hydatidiform mole and was treated with dilation and curettage. Because of persistent elevation of serum β human chorionic gonadotropin, the patient was treated with combination chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMACO) for high-risk gestational trophoblastic tumor. The patient's initial stage was IIc. The serum β human chorionic gonadotropin level returned to normal. Fourteen months later, the gonadotropin level again increased. The patient was treated with uterine curettage followed by vaginal hysterectomy. Despite further chemotherapy (with methotrexate and leucovorin, then oral etoposide), she died following metastasis of the tumor to the brain.

Only four other cases of human immunodeficiency virus (HIV) infection with choriocarcinoma have been reported. There is no evidence to date that gestational trophoblastic disease is more prevalent in patients with acquired immunodeficiency syndrome. HIV infection and other immunodeficiency states, however, can influence the course of treatment and outcome in these patients. The low CD4 count in HIV infection may lead to a poor outcome despite chemotherapy.

Key Words: Choriocarcinoma, acquired immunodeficiency syndrome, HIV.

Introduction

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) due to human immunodeficiency virus (HIV) infection is frequently associated with lymphoproliferative neoplasms, Kaposi's sarcoma, and some squamous carcinomas (cervical, vaginal, and vulvar). Other cancers are rare in AIDS patients (1). In this latter group are gestational trophoblastic tumors (GTT), which include a spectrum of diseases that arise from placental trophoblastic tissue after abnormal fertilization. Most GTTs result in a hydatidiform "molar" pregnancy characterized by the lack of a fetus, trophoblastic hyperplasia, edematous chorionic villi and a loss of normal villous blood vessels.

A total of four cases of choriocarcinoma in HIV-positive patients have been reported. Three such patients were first described by Ojwang and Otieno in Africa in 1992 (2). One patient received prolonged chemotherapy without remission, the second had a remission only after hysterectomy and chemotherapy, and the third had extensive metastatic disease in spite of low-risk factors (see the World Health Organization scoring system, Table 1). In 1998, Tangtrakul and Linasmita reported a case of an HIV-infected woman with choriocarcinoma presenting as a nasal mass (3). This patient had complete resolution of her disease following multiagent chemotherapy. No other cases have since been documented in the literature.

Case Report

A 26-year-old African American woman was admitted to the intensive care unit of a community hospital with a history of shortness of breath, and blood-tinged sputum for two to three days. Medical history included AIDS, HIV positive for three years, asthma, pulmonary tuberculosis, and pneumocystis pneumonia. The patient had delivered a normal full-term infant 8 months previously. On physical examination, the patient was afebrile, thin, tachypneic, with small, pea-sized cervical and axillary lymphadenopathy. The lungs revealed diffuse rhonchi and wheezing. The abdomen was soft but tender in the right lower quadrant.

The leukocyte count was 7100/mm^3, hemoglobin 11.2 g/dL, hematocrit 32.1%, and platelets 263,000/mm^3. Liver function tests and serum electrolytes were normal, and the CD4 count was 173/mm^3. The serum β-HCG level was greater than 5 million IU/L (normal = 0–10 IU/L). The serum T_3 and T_4 levels were 190 ng/dL (normal 59–174 ng/dL) and 16 μg/dL (normal 4.5–12 μg/dL) respectively.

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TABLE 1

*World Health Organization Prognostic Scoring System for GTT** (4)

Score Factor	0	1	2	4
Age	<35	>35		
Prior Pregnancy	Hydatidiform Mole	Abortion	Term	
Interval	<4 months	4 – 6 months	7 – 12 months	>12 months
Serum β-HCG (IU/L)	<1,000	1,000 – 10,000	10,000 – 100,000	>100,000
ABO blood group		O or A	B or AB	
Largest Tumor Size	< 3 cm	3 – 5 cm	> 5 cm	
Metastatic Sites	Lung	Spleen, kidney	GI tract, liver	Brain
# of Metastases		1 – 3	4 – 8	> 8
Prior Chemotherapy			1 drug	2 or more drugs

*GTT= Gestational trophoblastic tumors

The ultrasound of the pelvis showed that the uterus was enlarged (5 cm) with endometrial thickening and a small fluid collection. No yolk sac was seen. A chest X-ray revealed extensive bilateral alveolar infiltrates.

The diagnosis of hydatidiform mole was suspected. The patient was treated with dilation and curettage of her molar pregnancy. Histopathology revealed hydatidiform mole with features suggesting partial mole. The abnormal chest X-ray was interpreted as metastatic choriocarcinoma or AIDS-related pneumonia (e.g., pneumocystis pneumonia, pulmonary tuberculosis, pneumonia with cytomegalic virus). Bronchoscopy revealed an infectious cause (streptococcus). Since the patient was allergic to penicillin, the pulmonary infiltrates were treated with erythromycin, and trimethoprim and sulfamethoxazole.

Using the World Health Organization (WHO) (Table 1) prognostic scoring system for GTT, we found that our patient had a score greater than 7 based on the β-HCG level (5 million IU/L), tumor size (larger than 5 cm) in the uterus, ABO blood type group, and time interval (more than 4 months previously) since the antecedent pregnancy, and a full-term delivery 8 months previously.

Due to persistent elevation of serum β-HCG, and the high-risk prognostic score, one cycle of combination chemotherapy consisting of etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine was administered along with GCSF (granulocyte colony-stimulating factor) and erythropoietin. The β-HCG was initially greater than five million IU/L but decreased to normal within 4 weeks and remained normal after chemotherapy. No detectable residual disease was seen on ultrasound.

Fourteen months after the β-HCG levels had returned to normal, the serum β-HCG again increased (14.6 IU/L). The ultrasound of the pelvis showed no gestational sac, but the uterus was enlarged (6.5×4.5×4.3 cm) and a small amount of free fluid was detected in the cul-de-sac. The β-HCG progressively increased (to 387 IU/L), and despite uterine curettage, it remained elevated (59 IU/L). The patient subsequently underwent vaginal hysterectomy.

Histopathological exam of the uterus revealed several areas of choriocarcinoma. The patient was not compliant with her medications, and refused to have the full initial chemotherapy regimen with EMACO, since it made her quite sick. She received etoposide and cisplatin but had prolonged myelosuppression despite GCSF. These drugs were replaced by methotrexate and leucovorin, from which she experienced nausea and vomiting. Three months later, etoposide was again started; the patient complained of headache and was readmitted. Work-up revealed metastatic disease to the brain. Shortly thereafter, the patient died with respiratory distress following herniation of the brain.

Discussion

Gestational trophoblastic disease consists of a group of diseases (Table 2) which include complete and partial molar pregnancy, placental site trophoblastic tumor, and gestational choriocarcinoma; these have variable tendencies for local invasion and metastasis. Although persistent gestational trophoblastic tumor (GTT) most commonly follows a molar pregnancy, it may occur after any type of gestation (4). Most molar pregnancies spontaneously resolve after uterine evacuation. However, malignant trans-

TABLE 2
Characteristics of Complete and Partial Moles

Features	Partial Mole	Complete Mole
Karyotype	69XXY (90%)	46XX (90%)
Genetic parentage	Biparental	Paternal
Villous edema	focal	diffuse
Trophoblastic hyperplasia	focal	diffuse
Embryonic tissue	present	none
Persistent β-HCG	0.05%	20%

formation may occur in 10–20% of molar pregnancies. The common metastatic sites of GTT are the lungs (80%); vagina (30%); pelvis (20%); liver (10%); brain (10%); and bowel, kidney, and spleen (5% each). Persistent GTT is one human cancer that may respond very favorably to treatment even in the presence of widespread metastasis but may require more aggressive chemotherapy as well as surgery and/or radiation.

In 1976, Bagshawe described a scoring system intended to define the prognosis of patients with GTT (5). Most of the prognostic factors relate to tumor burden (HCG serum level, size and number of metastases), sites of metastasis, duration of disease, and degree of prior chemotherapy exposure and resistance. The World Health Organization (WHO) later published a modified prognostic scoring system in table form (Table 1) that reliably predicts the probability of resistance to chemotherapy (6). This scoring system included age, antecedent pregnancy, β-HCG level, size of the tumor, number and site of metastases, and prior chemotherapy. Several factors were associated with poor prognosis. One of these is the size of the tumor (mass greater than 5 cm) and a very high serum β-HCG level. Patients who exhibit metastases to the brain, liver, and intestines have a poorer prognosis than those who have metastases to other sites. Other factors which increase risk include persistent disease 4 months beyond the antecedent pregnancy, older than 39 years of age, maternal/paternal blood type, and failure to respond to a previous course of chemotherapy. The total score for a patient is obtained by adding the individual scores for each factor. A total score of 4 or less corresponds to low-risk disease, while a score of 5–7 is of intermediate risk. When the score is 8 or greater, the patient is considered to be at high risk and requires intensive combination chemotherapy to achieve remission. A patient is considered high risk when a combination of high-risk factors and high score is present.

While GTT can be cured with chemotherapy, 10–25% of patients with metastatic disease die of this cancer. Choriocarcinoma is a malignancy which has an excellent prognosis, with 93% of patients without metastatic disease achieving remission using single agent chemotherapy and 87% of patients with metastatic disease achieving remission using combination chemotherapy. The administration of combination chemotherapy with the selective use of surgical and radiation therapy in high-risk patients has resulted in dramatic improvements in survival. Remission rates, even for patients with higher scores, approach 90% in some series (7–9). Nonetheless, some patients are resistant to current combination chemotherapy despite intensive treatment.

DuBeshter and Berkowitz reviewed the records of 51 patients with metastatic gestational trophoblastic tumor (11). The clinical characteristics and therapy of patients who died were compared to those of patients who attained remission, to identify parameters associated with treatment failure. The presence of liver, brain, or intestinal metastases and the failure of prior chemotherapy were found to portend a poor prognosis. They did not find, as had the WHO, that markedly elevated β-HCG levels, time interval longer than 4 months from the antecedent pregnancy to treatment, and post-term choriocarcinoma were independently associated with treatment failure. The mean prognostic score and the mean number of high-risk factors for patients who died were 13 and 3, as compared to 7 and 2, respectively, for patients who achieved remission. Intensive chemotherapy regimens need to be administered to patients with liver, brain, or intestinal metastases, failed prior chemotherapy, or a high prognostic score. Remission rates of patients receiving triple therapy with methotrexate, actinomycin-D, and cyclophosphamide (MAC) are poor, resulting in only 50% complete responses. However, a remission rate of 83% is possible in patients whose disease includes high-risk factors and elevated scores, using a combination regimen which includes etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine (10–12).

In AIDS patients, the HIV infection selectively attacks T-derived lymphocytes of the helper/inducer subtype, causing qualitative and quantitative deficiencies in both cellular and humoral immunity (13). There is global immune depression. Trophoblastic tissue, which is an allograft, exhibits transplantation antigens and invades maternal tissue to form the maternal surface of the placenta. It is not rejected by the maternal immune response at this site. While trophoblastic emboli are shed into the maternal serum during normal pregnancy, they are effectively destroyed by the mother's immune response and do not result in any neoplastic process. Theoretically, it is possible that in AIDS patients, a failure of an immune response to destroy these tumor cells leads to metastatic lesions, thus predisposing such patients to the development of choriocarcinoma. When chemotherapy is given, there is an initial reduction of tumor mass. Further reduction in tumor mass is enhanced by the effect of a normal immune system. This forms the basis for the use of immunotherapy combined with chemotherapy (14). There is reason to believe that suppression of cell mediated immunity by HIV infection can significantly hamper effectors of tumor immunity (2, 13). It has been recommended that HIV infection be included in the list of WHO prognostic factors for choriocarcinoma (2). In patients with AIDS, the effectiveness of the immune system is suboptimal; thus response to chemotherapy can be expected to be poor (2). The benefits/risks of further immunosuppression with chemotherapy versus malignancy progression must be carefully weighed in these patients and may require that dosage be lowered and used in conjunction with administration of GCSF if neutropenia is present.

In three of the four cases reported in the literature of HIV infection with choriocarcinoma, as described by Ojwang et al. (2), one had a prolonged course of chemotherapy without remission; a second responded only after hysterectomy combined with chemotherapy; and the third had extensive metastases with tumor in unusual sites despite low-risk factors. Since all three patients were lost to follow-up after initial treatment, no long-term information is available. Because the clinical manifestations of the three cases were aggressive, HIV infection was proposed to be a poor prognostic risk factor for GTT. CD4 counts in these patients were not reported. The fourth case, of an HIV-positive woman with choriocarcinoma, was reported by Tangtrakul et al. (3) and presented with a nasal mass and a normal CD4 count. The normal CD4 count may explain why the patient tolerated the multiagent chemotherapy and achieved a complete remission. In our patient, the CD4 count was low.

As the AIDS epidemic continues to spread, we may see an increased incidence of GTT. We need to have a better understanding of the interaction between HIV and GTT. The key to any poor response to chemotherapy may be the extent to which the CD4 count is suppressed. In the parallel situation of AIDS-related lymphoma, chemotherapy also is not well tolerated and these patients have a poor outcome when their CD4 count is below 200/mm^3.

HIV-positive patients with choriocarcinoma present challenges in diagnoses. Metastatic lesions in the lung or brain must be differentiated from disease due to infectious etiologies. With regard to our patient, the role played by HIV is uncertain. Her noncompliance with treatment might itself have led to a poor outcome.

Conclusion

More data are needed to determine the appropriate management of choriocarcimoma in the HIV-positive patient. With only a few published cases in the literature, it is difficult to draw any definitive conclusions. To date, there is no evidence that gestational trophoblastic tumor is more prevalent in AIDS patients.

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Coronary Artery Disease in Women:

A Review of Emerging Cardiovascular Risk Factors

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Abstract

Coronary heart disease is the leading cause of death and disability in both men and women in industrial nations. From 1988 to 1998, the death rate from coronary heart disease actually declined 26.3%, resulting to some extent from the recognition and treatment of modifiable risk factors. The clinical observation that traditional risk factors for atherosclerosis cannot account for all patients who develop coronary heart disease or stroke has stimulated interest in reevaluating these factors and considering other determinants of pathogenesis. Our understanding of atherogenesis has evolved from a focus on lipid deposition within the arterial wall causing obstruction to the broader view of an inflammatory process which involves specific cellular and molecular responses to endothelial dysfunction. As a consequence, "emerging" cardiovascular risk factors and preventive strategies have been proposed. For example, there is an increasing understanding of the pathology of hypercholesterolemia and the benefits of lipid-lowering medications (specifically statins), the role of oxidative stress, and antioxidant, homocysteine, and hypercoagulable states.

This review examines the data for these and other emerging risk factors, with specific attention to gender differences.

Key Words: Coronary artery disease, coronary heart disease, women, atherosclerosis, pathophysiology.

Introduction

CORONARY HEART DISEASE (CHD) remains the leading cause of death and disability in both men and women in industrial nations. In 1997, a total of 466,101 deaths in the United States were attributed to CHD. Approximately half of them were women (1). However, the common misperception that CHD is a "man's disease" remains. A survey by the American Heart Association reported that only 8% of the women questioned recognized that heart disease and strokes are the leading cause of death among women, and that cardiovascular disease kills more women each year than the next 16 causes of death combined. One in two women dies of heart disease or stroke, while only one in 25 dies of breast cancer (2).

During the decade 1988 – 1998, the death rate from CHD actually declined 26.3% (1). This resulted in part from the recognition and treatment of modifiable risk factors such as diabetes, hypertension and tobacco use. While most traditional risk factors are similar in men and women, there are differences in risk factors between the two sexes, as well as differences in the magnitude of the effects of these risk factors. For example, diabetes, a known risk factor for CHD, is a stronger risk factor in women than in men. CHD mortality rates are approximately 3 – 7 times greater for diabetic women than for non-diabetic women. In comparison, the mortality rate is only 2 – 3 times greater for diabetic men than for non-diabetic men (3).

The clinical observation that traditional risk factors for atherosclerosis cannot account for all patients who develop CHD or stroke has stimulated interest in reevaluating the risk factors and considering other determinants of pathogenesis. Our understanding of atherogenesis has evolved from a focus on lipid deposition within the arterial wall causing obstruction, to the broader view of an inflammatory process which involves specific cellular and molecular responses to endothelial dysfunction. As a con-

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sequence, "emerging" cardiovascular risk factors and preventive strategies have been proposed. For example, there is an increasing understanding of the pathology of hypercholesterolemia and the benefits of lipid-lowering medications (specifically statins), the role of oxidative stress, and antioxidant, homocysteine, and hypercoagulable states. This review examines the data for these and other emerging risk factors, with specific attention to gender differences.

Pathogenesis

One of the earliest events in the development of atherosclerosis is thought to be endothelial dysfunction (4), the causes of which are thought to include elevated and oxidized low-density lipoproteins (LDL), free radicals from tobacco, hypertension, diabetes mellitus, acquired and genetic hypercoagulable states, and infectious organisms. These factors may also act in synergy. Endothelial dysfunction in turn results in a series of compensatory responses that alter the homeostatic properties of the endothelium (4–6). The atherosclerotic lesion progresses from the early fatty streak to plaque rupture if the insult is not removed and the inflammatory response continues unabated.

Endothelial dysfunction is characterized by a number of changes. Cell surface markers involved in adhesion — such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) — are up-regulated, and production of cytokines, chemokines and other growth factors is increased. As a result, there is increased adhesiveness of platelets and leukocytes to the endothelium, increased vascular permeability and a local procoagulant state. These factors contribute to the recruitment from the circulation of mononuclear leukocytes and their migration into the subendothelial space. Foam cells are formed when monocyte-derived macrophages take up LDL. Both the macrophages and T lymphocytes in turn produce cytokines, including interleukin-1 (IL-1) and interleukin-6 (IL-6), which increase cellular recruitment and promote smooth muscle cell proliferation. The fatty streak progresses into an intermediate lesion, which is characterized by a fibrous cap that forms over the atheroma and separates the cells, lipids and necrotic cell debris from the vascular lumen. The artery wall thickens and attempts to compensate by dilatation. Continued inflammation results in increased recruitment of activated inflammatory cells, causing the release of enzymes such as metalloproteinases, and the manufacture of tissue factor. Ultimately, further damage of the arterial wall occurs, and in some cases rupture of a vulnerable plaque and thrombus formation, causing what is known today as the acute coronary syndrome (7). Other factors that may contribute to the unstable coronary syndrome include a hypercoagulable state and impaired responsiveness to endothelium-dependent vasodilators in diseased portions of the coronary arteries.

Markers of Inflammation

These new insights into the role of inflammation in the pathophysiology of atherosclerosis have led several investigators to examine mediators and markers of inflammation in patients with coronary heart disease. A number of studies have shown elevations in the levels of high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA) protein, fibrinogen, cellular adhesion molecules-1 (ICAM-1), and cytokines (IL-6, tumor necrosis factor-alpha). One of the hurdles in performing these studies has been the difficulty in developing standardized assays. Because of the availability of a reliable and sensitive assay, C-reactive protein (CRP) has been the most studied of the inflammatory markers.

It has been demonstrated that high-sensitivity C-reactive protein (hs-CRP) levels may be useful in predicting CHD as well as other vascular events, e.g., stroke and peripheral vascular disease (8). This has been validated by findings in a number of different populations, ranging from patients at low risk for CHD to those with overt CHD, as well as in women and in the elderly. A prospective, nested case-control study of the Women's Health Study (WHS) assessed the risk of cardiovascular events associated with levels of markers of inflammation among 122 apparently healthy postmenopausal women (9). The markers of inflammation included hs-CRP, SAA, IL-6, and soluble ICAM-1. This study demonstrated that women with the highest hs-CRP at baseline had a 5-fold increase in the risk of any vascular event and a 7-fold increase in risk of myocardial infarction (MI) or stroke. Similarly, hs-CRP levels were also measured in the Physician's Health Study (PHS), a primary prevention study that randomized male physicians to aspirin vs. placebo (10). In the more than 8 years of follow-up, individuals who went on to have coronary events or stroke had higher levels of hs-CRP than did those who did not have a vascular event. Those with the highest hs-CRP levels had three times the risk of myocardial infarction and twice the risk for stroke compared to those with the lowest hs-CRP. As in the WHS, the risk estimates were independent of other traditional cardiovascular risk factors. Importantly, CRP has also been shown to add to the predictive value of lipid parameters in determining the risk of a first MI. In the PHS, baseline levels of CRP, total cholesterol, and high-density lipoproteins (HDL) correlated with myocardial events. Multivariate analysis models incorporating CRP and lipid parameters provided a significantly better method of predicting risk than did models using lipids alone (11).

Additional studies have shown the prognostic value of hs-CRP in men and women with coronary disease. In a small prospective study of 32 patients (26 men and 6 women), Liuzzo et al. demonstrated that patients with unstable angina and elevated hs-CRP (≥ 0.3 mg/dL) had a higher incidence of ischemic episodes and more adverse outcomes, including death, myocardial infarction and/or emergent revascularization, compared to patients with lower levels of hs-CRP (12). Furthermore, Ferreiros et al. showed a strong relationship between elevated CRP, especially levels at time of discharge, and 90-day outcome (defined as death from any cause, myocardial infarction and/or refractory angina) compared to patients with lower levels of CRP (13).

The role of hs-CRP as a marker has also been examined in the context of therapeutic interventions. A nested case-control study of Cholesterol and Recurrent Events (CARE), a secondary prevention trial that randomized patients to pravastatin vs. placebo, suggested that treatment with pravastatin decreases the level of hs-CRP in both men and women. This supports the theory that hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors have benefits beyond lipid-lowering effects (14). An analysis of the PHS found that the use of aspirin was associated with a significant reduction in the risk of first myocardial infarction in patients with the highest levels of CRP, perhaps reflecting its anti-inflammatory effects (10).

Interestingly, the median levels of hs-CRP in the WHS were slightly higher than those in the PHS, and the absolute risk associated with the elevated levels of hs-CRP in this study of women was greater than that observed in prior studies of men (15). Estrogen appears to increase CRP levels. Four markers of inflammation (CRP, soluble E-selectin, von Willebrand factor antigen, and coagulation factor VIIIc) were studied in 365 postmenopausal women from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study, a randomized, placebo-controlled trial that examined the effects of four hormone preparations on cardiovascular risk factors. All four of the hormone preparations were associated with an increase in CRP levels (16). Similarly, in another study of 493 healthy postmenopausal women with mean age of 51 years, median CRP levels were twice as high among women taking hormone replacement therapy (HRT) (17). Neither study was designed to assess clinical endpoints. These studies may help explain the results of the Heart and Estrogen/Progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis (ERA) trials. The HERS trial found no reduction in risk of nonfatal myocardial infarction and death from coronary heart disease among women with established CHD (average age 65 years) who were treated with conjugated estrogen plus medroxy-progesterone acetate (18). The ERA trial demonstrated that although HRT produced significant reductions in LDL cholesterol and increases in HDL cholesterol, there was no effect on the progression of CHD by coronary angiogram (19). This raises the possibility that pro-inflammatory effects of HRT may cause plaque instability that offset the benefits of HRT on lipids. Further investigation needs to be done to determine the significance of this gender difference.

The exact mechanism by which a stable plaque converts into an unstable lesion and the role of CRP in the acute coronary syndrome are both unclear. It is hypothesized that CRP can act as a procoagulant or even as an inducer of the immune system. Conversely, CRP could simply be an inflammatory marker that is the result of whatever inflammatory process is occurring. Whatever the case might be, based on epidemiological studies, inflammatory parameters like hs-CRP level may help determine which clinically stable patients are at risk for future cardiac events, and guide future treatment strategies.

Risk Factors

Hyperlipidemia

The association between hypercholesterolemia and CHD was first noted in the 1930s by Muller et al. (20), who reported premature coronary heart disease in patients with hereditary xanthomatosis. Since then, a number of large epidemiological studies have confirmed the relationship between high cholesterol and CHD in men and women. However, gender differences exist in the patterns of cholesterol associated with increased risk. For example, the level of total cholesterol that correlates with increased risk for CHD may be higher in women than in men, in part secondary to higher HDL levels seen in women (21).

While the Framingham Heart Study (21) demonstrated that low levels of HDL cholesterol predict an increased incidence of CHD in men and women, it is independent of other CHD risk factors, including LDL (22). Several studies have shown that increasing HDL lowered CHD events in men and women, independent of LDL (The Lipid Research Clinics Coronary Primary Prevention Trials using cholestyramine, Helsinki Heart Study using gemfibrozil, and The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group also using gemfibrozil) (23–25). As in the male population, a particularly strong relationship between low HDL cholesterol and CHD risk is also found in women. A National Heart, Lung, and Blood Institute workshop pooled data on different lipoproteins from several cohort studies of a total of approximately 86,000 women from different populations. Among younger women (< 65 years) there was an increased relative risk associated with elevated total and LDL cholesterol, and low HDL. However, in older women (> 65 years, and therefore a group at higher risk for CHD), only low HDL of < 50 mg/dL was significantly associated with increased CHD mortality (26). This was confirmed in a study by Corti et al. of 2,527 women who were 71 years of age or older (27). In those individuals whose HDL cholesterol levels were less than 35 mg/dL, the relative risk of CHD mortality was twice that of women with HDL cholesterol levels greater than 60 mg/dL, in the 4.4 years of follow-up (27). In men whose HDL levels were less than 35 mg/dL, the relative risk of CHD mortality was close to 5 times that of men with HDL greater than 60 mg/dL.

HDL is thought to exert its positive effects via its role as a reverse cholesterol transporter and antioxidant, its maintenance of endothelial function, and its protection against thrombosis (28). Low HDL cholesterol is affected by such factors as heredity, tobacco smoking, obesity, lack of exercise and certain medications such as beta-blockers. Estrogen appears to elevate HDL cholesterol levels, which may explain why premenopausal women have higher levels than men and exhibit a lower incidence of CHD before the age of 50. Treatment of low HDL includes niacin, gemfibrozil and estrogen.

Triglycerides

More support for high triglycerides as an independent CHD risk factor has accumulated in recent years. There is some evidence to suggest that triglycerides are an important risk factor in women 50–69 years of age and in patients with non-insulin-dependent diabetes (29, 30). In one analysis of 17 studies (46,413 men and 10,864 women), elevated triglyceride levels were associated with an increased cardiovascular risk of 76% in women and 32% in men (31). After adjustment for HDL and other risk factors, the increased risks were decreased but remained statistically significant (37% in women, 14% in men). Another study of myocardial infarction survivors showed that the risk of MI was 6.8 times higher in those with the highest triglyceride levels. The risk was even more significant (16-fold) in those with the highest triglycerides-to-HDL ratio (32). High triglycerides also seem to be more important in women with non-insulin-dependent diabetes mellitus. Diabetic women in the highest tertile of triglyceride levels have a 200-fold increase in CHD prevalence, in contrast to diabetic men whose risk increases 3-fold (33). Current treatment strategies for high triglycerides include non-pharmacologic therapy, in particular, diet, exercise, weight control, and alcohol reduction. Pharmacologic approaches that have been effective in reducing high triglycerides include niacin, fibrates, and to a lesser extent statins.

Clinical Trials

Several clinical trials have demonstrated that lowering cholesterol decreases coronary artery disease morbidity and mortality, slows the progression of atherosclerotic lesions and perhaps leads to their regression. The degree to which these results can be extrapolated to women is unknown, since most studies either excluded women or had too few women to be statistically significant. Review of primary prevention trials that included women yielded four studies. Two studies (the Finnish Mental Hospital Study and the Minnesota Coronary Survey) examined dietary intervention in reducing total cholesterol levels. The other two (the Upjohn Colestipol Study and the Air Force/Texas Coronary Atherosclerosis Prevention Study — AFCAPS/TexCAPS) examined pharmacologic intervention. The Finnish Mental Hospital Study (34) randomized 6,435 women in mental institutions who were older than 15 years of age to a cholesterol-lowering diet or a control diet. Women in the treated group had a 12% reduction in their serum cholesterol, but there were no statistically significant reductions in CHD deaths in the treated group. The Minnesota Coronary Survey (35) randomized 4,664 women to a low-saturated-fat, high-polyunsaturated-fat, low-cholesterol diet or a regular control diet. Serum cholesterol decreased by 15% in the treated group, but there were no significant differences in events such as acute myocardial infarctions, sudden deaths and silent myocardial infarctions between the two groups. The Upjohn Colestipol Study (36) randomized 1,184 women to colestipol or placebo and followed them for up to three years. Total cholesterol decreased in the treated group; however, there was no significant difference in the mortality rates between the two groups. More recently, the AFCAPS/TexCAPS (37), the first trial to demonstrate the efficacy of primary prevention in women, randomized 6,605 patients (997 women) with "average" cholesterol and no history of CHD to placebo vs. lovastatin. This study showed that the effect of treatment with lovastatin on the rate of first acute major coronary events was greater in women than in men (46% vs. 37% reduction in relative risk).

Secondary prevention trials appear to show benefits of lipid lowering in women. The CARE trial randomized 4,159 CHD patients (3,583 men, 576 women) with cholesterol levels of less than 240 mg/dL to receive either 40 mg/day of pravastatin or placebo. The women had twice the reduction in risk of recurrent cardiovascular events, including reduction in CHD death or nonfatal MI, coronary artery bypass grafting (CABG), or angioplasty (PTCA), and combined cardiovascular events, when compared to men (46% reduction rate for women vs. 20% for men) (38). The Scandinavian Simvastatin Survival Study (4S) randomized 4,444 patients (827 women) with angina pectoris or prior myocardial infarction and elevated cholesterol (213–310 mg/dL) to simvastatin vs. placebo. There was a 34% reduction for major coronary events in women vs. 42% for men (39).

Mechanism of Treatment Benefits

It is not entirely clear how therapy with statins improves outcome. The decrease in incidence of events is far more significant than the degree of plaque regression, as evaluated by coronary angiogram (40). Furthermore, the benefit of lipid lowering, which must occur before significant regression can occur, is seen in as little as six months. The beneficial effects of statins on clinical events, in addition to their role in the regression of coronary lesions, may involve a therapeutic role in inflammation. Possible nonlipid mechanisms include plaque stabilization, reversal of endothelial dysfunction, inhibition of monocyte recruitment, inhibition of smooth muscle proliferation, decrease in thrombogenicity and reduction in inflammation after MI (40). There is even some evidence that statins may have an antioxidant effect (41).

Lipoprotein (a)

Lipoprotein a (Lp(a)) is a modified form of LDL, in which a large glycoprotein, apolipoprotein (a), is covalently bound to apo B by a disulfide bridge. The apo (a) chain shares partial homology with plasminogen, a plasma protein that dissolves blood clots when activated. Because of this structural similarity to plasminogen, it is hypothesized that Lp(a) interferes with fibrinolysis by competing with plasminogen binding to molecules and cells (42). This causes impairments in plasminogen activation, plasmin generation, and fibrinolysis. Lp(a) also binds to macrophages via a high-affinity receptor that promotes foam cell formation and deposition of cholesterol in atherosclerotic plaques. Lp(a) is increased in renal disease. Its levels also fluctuate in states of hormonal change, such as that which occurs in diabetes, after menopause, and with pregnancy.

There is conflicting evidence as to whether Lp(a) is an independent risk factor for CHD. A positive association between Lp(a) and CHD has been shown in many retrospective trials, but the data in prospective trials have not been as convincing. For example, the Physicians' Health Study, Helsinki Heart Study, and the Quebec Cardiovascular Study showed no evidence of a positive association between baseline plasma concentration of Lp(a) and future vascular events (43). This contrasts with findings in the Lipid Research Study, the British United Provident Association and the Stanford Five City Project, which did show positive graded associations between Lp(a) and risk for CHD. The Framingham Heart Study, a major study of 3,103 women, did find Lp(a) to be an independent predictor of MI and cardiovascular disease (44). In this study, Lp(a) was measured at baseline by electrophoresis. At a mean follow-up of 12 years, multivariate-adjusted relative risk (RR) estimates were 2.37 for MI, 1.61 for CHD, and 1.44 for total cardiovascular disease.

Lp(a) has also been studied as a risk factor for restenosis after PTCA as well as CABG, with conflicting results. In one angiographic study of 71 patients (23 women) who underwent successful PTCA, the incidence of restenosis was significantly higher in patients with Lp(a) of more than 30 mg/dL, than in those with Lp(a) of less than 30 mg/dL (65% vs. 26%; $p<0.01$) (45). This was confirmed in another angiographic study of 80 patients (22 women). Serum Lp(a) levels in the restenosis group were significantly higher than in the nonrestenosis group (29 mg/dL vs. 17 mg/dL) (46). This correlation, however, was not seen in other studies. In an angiographic study of 305 patients (58 women), no significant association was determined between serum levels of lipoproteins and luminal loss (47). Similar conflicting results were seen in patients who underwent CABG with vein grafts. In a study by Hoff et al. of 167 patients (18 women), 92% of the patients with Lp(a) levels of 31.6 mg/dL or above demonstrated vein graft stenosis (48). A more recent study of 353 patients (56 women), however, did not show that serum Lp(a) level correlated with vein graft occlusion five years after CABG surgery (49). Because of the inconsistency of prospective data, screening for Lp(a) is usually done only in specific high-risk settings (i.e., premature CHD or a family history of CHD) or in patients without apparent traditional risk factors. Drugs used to treat Lp(a) are niacin and estrogen.

Oxidative Stress — The Role of Antioxidants

As stated previously, oxidative modification of LDL is an important step in the pathogenesis of atherosclerosis. Several animal models have demonstrated that antioxidants decrease oxidation of LDL and reduce plaque formation (50). There is also evidence that antioxidants inhibit monocyte adhesion, protect against the cytotoxic effects of oxidized LDL, inhibit platelet activation, and protect against endothelial dysfunction associated with atherosclerosis, by preserving endothelium-derived nitric oxide activity. Epidemiological studies have reported that increased intake of antioxidants, specifically vitamins E and C, via diet or supplements, is associated with decreased morbidity and mortality of coronary artery disease.

There is conflicting evidence for vitamin E supplementation in the prevention of CHD. In the Nurse Health Study, increased vitamin E intake was associated with less cardiovascular disease (51). The study was a prospective cohort study that assessed intake of vitamin E (along with vitamins A and C) in 34,486 women with no history of CHD. Intake of vitamins A and C did not have a significant association with risk of death from CHD. The Cambridge Heart Antioxidant Study (CHAOS) was a secondary prevention study that randomized 2,002 patients with coronary atherosclerosis to vitamin E 800 IU or 400 IU daily, or to placebo (52). This study reported marked reductions in nonfatal myocardial infarction and in the combined endpoint of nonfatal MI and cardiovascular death of any major cardiovascular event after one year of treatment. No effect on cardiovascular death was observed. However, this trial had many methodological problems (e.g., the study groups were not balanced at baseline and there was a short duration of follow-up).

Conversely, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) design trial, another secondary prevention trial, did not show statistically significant reductions in clinical events when patients were treated with 300 mg/day of vitamin E (53). Recently, the Heart Outcomes Prevention Evaluation Study (HOPE) randomized 9,541 patients (2,545 women and 6,996 men) who were at high risk for cardiovascular disease to vitamin E 400 IU/day, ramipril 10 mg/day, both, or none (placebo). There was no clear benefit to patients treated with vitamin E for a mean of 4.5 years in reduction of the incidence of cardiovascular death, myocardial infarction, and stroke (54).

Other antioxidants have been evaluated, with equally conflicting results. A number of epidemiological studies have evaluated the influence of supplemental vitamin C intake in the primary prevention of CHD. The Atherosclerosis Risk in Communities Study (ARIC Study) noted an inverse relationship between vitamin C intake and the average carotid artery wall thickness in more than 4,000 patients who were 55 years of age or older (55). The National Health and Nutrition Examination Survey (NHANES) (56) showed that men with the highest vitamin C intake (> 50 mg/day) had significantly lower all-cause mortality and cardiovascular mortality rates. In women there was an insignificant all-cause mortality reduction, but cardiovascular deaths were significantly less frequent (56). On the other hand vitamin C supplementation did not affect the risk of myocardial infarction or coronary death in the Nurses' Health Study or in the PHS (57, 58). The role of vitamin C in secondary prevention has not been well studied, but the available data do not support its use. For example, in the Cholesterol Lowering Atherosclerosis Study (CLAS), supplemental vitamin C use did not improve angiographically determined lesion progression (59).

Homocysteine

Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. Elevations of plasma homocysteine have been associated with increased age, menopause, genetic defects in the enzymes involved in homocysteine metabolism (e.g., methylene tetrahydrofolate reductase deficiencies), nutritional deficiencies in vitamin co-factors (e.g., folate, vitamin B12), and other systemic diseases (e.g., renal failure, liver disease) (60). The proposed pathophysiologic mechanisms of hyperhomocysteinemia include endothelial injury and dysfunction followed by platelet activation and thrombus formation (60).

In most prospective and case-control studies of men and women, hyperhomocysteinemia appears to be an independent risk factor of atherothrombotic vascular disease. In a case-control study of the PHS, men with homocysteine levels above the 95th percentile had a 3-fold increase in the risk of myocardial infarction compared to those in the lower 90th percentile (61). The authors estimated that 7% of the observed myocardial infarctions could be attributed to hyperhomocysteinemia. One population-based, case-control study compared 79 women younger than 45 years of age who had a myocardial infarction, with 386 normal controls. This study showed that myocardial infarct patients had a higher mean plasma homocysteine level (13.4 µmol/L vs. 11.1 µmol/L) and lower mean folate level (12.4 nmol/L vs. 16.1 nmol/L) (62). Similarly a prospective, nested case-control study of 122 WHS participants who had experienced cardiovascular disease showed that case subjects had a higher baseline homocysteine level (14.1 µmol/L vs. 12.4 µmol/L) (63). A meta-analysis of 27 nonrandomized studies demonstrated that each 5 µmol/L increment increase in homocysteine levels was associated with 1.6- and 1.8-fold increased CHD risks in men and women, respectively (64). In one study of 587 patients (approximately 20% women) with documented CHD who were followed for 4.6 years, mortality increased in patients with homocysteine levels greater than 15 µmol/L (65). A graded effect has also been demonstrated between homocysteine concentrations and the risk of coronary artery disease or cerebrovascular accident as well as mortality from CHD (61, 66–68).

Gender differences in circulating homocysteine concentrations have been reported (69). In the Third National Health and Nutrition Examination Survey, total homocysteine level was compared among population subgroups differing in estrogen status. Premenopausal women (17–54 years old) had lower mean homocysteine levels when compared to similarly aged men (8.1 µmol/L vs. 8.9 µmol/L). Women aged 17–44 years who were pregnant had lower mean homocysteine levels than did those who were not pregnant and not using oral contraceptives (6.0 µmol/L vs. 8.1 µmol/L). The homocysteine levels of estrogen-using women older than 55 years of age was slightly decreased when compared to nonestrogen users of similar age (9.5 µmol/L vs. 10.7 µmol/L). Men in the same age group also had slightly elevated homocysteine levels (10.4 µmol/L). The authors suggested that higher estrogen status is associated with a decreased homocysteine level.

Treatment of hyperhomocysteinemia varies with the underlying cause, but generally is related to vitamin supplementation with folic acid, pyridoxine, and vitamin B12. Although there are some data that suggest that treatment with folic acid can improve arterial endothelial function in adults with hyperhomocysteinemia, the effect on cardiovascular and venous thromboembolic disease of lowering homocysteine remains unknown (70). More studies will have to be performed to evaluate the clinical efficacy of therapeutic interventions before widespread screening and treatment of patients with atherosclerotic vascular disease can be recommended.

Obesity

The Framingham data has documented that obesity is an independent risk factor for CHD for both sexes (71, 72). Traditionally, women are defined as obese when their bone mass index (BMI) exceeds 27 kg/m^2. Different patterns of obesity appear to correlate to CHD incidence. An analysis of the data of the Nurses' Health Study showed that higher waist:hip ratio and greater waist circumference were associated with increased risk of CHD. If waist:hip ratio was 0.88, the adjusted relative risk (RR) of CHD death or myocardial infarction was 3.25 (vs. waist:hip ratio < 0.72). A waist circumference of 38 inches was associated with an adjusted RR of CHD death and myocardial infarction of 3.06 (73). The Iowa Women's Health Study was a cohort study of 31,702 women aged 55–69 years who were free of cancer, heart disease, and diabetes. Abdominal obesity as measured by waist:hip ratio appeared to be an independent risk factor for total mortality. Abdominal obesity when combined with high body mass index was found to be an important risk factor for CHD-related mortality or incident. Abdominal obesity appeared to be associated with hyperinsulinemia, dyslipidemia, hypertension and impaired fibrinolytic capacity, all of which increase the risk of CHD (74). Higher BMI was also found to be associated with higher CRP levels among 16,161 participants (8,678 women) 17 years of age or older, suggesting a state of low-grade systemic inflammation in overweight persons. Both overweight (BMI 25–29.9 kg/m^2) and obese (BMI > 30 kg/m^2) participants were more likely to have elevated CRP levels than their normal-weight counterparts (BMI < 25 kg/m^2). After adjustment for potential confounders, including smoking and health status, the odds ratio of elevated CRP was 6.21 (95% CI: 4.94–7.81) for obese women compared with 2.13 (95% CI: 1.56–2.91) for obese men (75). These data are of great concern, given the trend in increasing body weight in the United States over the past decade, especially among women (76). Currently, it is estimated that more than one-third of all American women can be classified as obese.

Sedentary lifestyle is a known risk factor for CHD. In a meta-analysis, there was a 2-fold increase in risk in CHD mortality in persons with sedentary vs. active occupation (77). An observational cohort study of 32,421 patients (22% women) showed that among women, low fitness and tobacco use were independent mortality predictors (78). This was supported in the recently published analysis of the Nurses' Health Study, in which women who adhered to a lifestyle involving diet, exercise, and abstinence from tobacco use had a very low risk of CHD (79). In a cohort study of the same Nurses' Health Study, brisk walking was associated with fewer coronary events (80). This underscores the importance of behavior modification in addition to pharmacological approaches in the prevention of CHD.

Hypercoagulable States

Rupture of an unstable plaque with formation of an occlusive thrombus is an important component in the pathogenesis of the acute coronary syndrome. In recent years, several studies have examined alterations in coagulation and fibrinolysis as risk factors for CHD. The largest body of evidence of an association between a hemostatic factor and CHD has been accumulated for fibrinogen. Fibrinogen increases plasma viscosity, promotes platelet aggregation, and stimulates smooth muscle proliferation. All of these properties may explain the mechanisms by which fibrinogen is thought to mediate its pro-atherogenic effects.

A meta-analysis of six prospective epidemiological studies that included a total of 92,147 persons demonstrated that an increase in the fibrinogen level was associated with an increased risk of subsequent MI or stroke (81). Persons with fibrinogen levels in the highest tertile had 2.3 times the relative risk of those in the lowest tertile. Of the six studies, only one, the Framingham Heart Study, included women. For women, the fibrinogen risk ratio was greatest only for CHD. In contrast, the risk ratio was greatest for stroke, intermediate for myocardial infarction, and smallest for peripheral vascular disease in men. The Atherosclerosis Risk in Communities (ARIC) Study followed 14,477 patients (> 50% of the participants were women) in the 45–64-year-old range without history of CHD for approximately 5 years. Increased fibrinogen was associated with a higher likelihood of CHD; in men the RR was 1.48 and in women it was 1.21. The highest versus lowest quintile RR's were 3.66 in men and 3.50 in women. In a multivariate analysis, factor VIII, von Willebrand factor and white blood cell count, as well as fibrinogen, were associated with total mortality (82). A more recent meta-analysis of 18 prospective fibrinogen studies indicated that, in comparing the fibrinogen levels of the highest and lowest tertiles, the CHD risk ratio was 1.8 (83). High fibrinogen levels in patients with chronic stable angina also predicted subsequent acute coronary events (84).

Fibrinogen levels appear in part to be genetically determined (85). Women tend to have higher levels than do men. Plasma fibrinogen increases with menopause, pregnancy, and the use of oral contraceptives; treatment with hormone replacement therapy (HRT) lowers this rise (86). Tobacco users have consistently been found to have high fibrinogen levels. Diabetics also appear to have elevated levels of fibrinogen as well as factor VII and anti-thrombin III. A prospective cohort study of 1,676 middle-aged persons (57% were women) with diabetes and no history of CHD showed that levels of albumin, fibrinogen, von Willebrand factor, factor VIII activity and leukocyte count were predictors of CHD (87). Pharmacologic intervention with ticlopidine, a drug that inhibits the adenosine diphosphate (ADP)-induced aggregation of blood platelets, has been shown to reduce fibrinogen level in patients with CHD, stroke, and peripheral vascular disease (88–90).

The fibrinolytic system is responsible for the removal of fibrin from the circulation. It consists of plasminogen, which is converted to its active form, plasmin, by plasminogen activators, including tissue plasminogen activator (tPA). Inhibitors of the system include plasminogen activator inhibitor type I (PAI-1). Since most of the tPA antigen measured is complexed with PAI-1 and is inactive, high levels of tPA antigen in association with high levels of PAI-1 reflect impairment of the fibrinolytic system. This impaired fibrinolytic system has been studied as a possible risk factor for CHD. High levels of plasma PAI-1 and tPA have been associated with CHD (91). In a prospective nested case-control study in which 78 cases and 156 controls were matched for age, sex, and sampling time, patients with a history of myocardial infarction had significantly higher PAI-1 and tPA levels (92). In a subset of the ARIC cohort, high levels of PAI-1, tissue-tPA, and D-dimer were associated with increased thickness of the carotid artery, which was used as an index of early atherosclerosis (93). This was supported by the European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study on the role of fibrinolysis and MI. The study included 3,043 patients with angina pectoris and angiographically verified coronary arteriosclerosis. It provided substantial documentation of an association between high plasma concentration of tPA and the risk of acute coronary syndromes (94).

Lifestyle modifications such as tobacco cessation and exercise appear to help improve the fibrinolytic profile. In addition, several studies have shown that HRT decreases PAI-1. In a double-blind, randomized, placebo-controlled trial, the short-term effects of oral 17-beta-estradiol were assessed in 40 postmenopausal women with non-insulin-dependent diabetes mellitus (NIDDM). Both total PAI-antigen and active PAI-1 antigen concentration decreased significantly during HRT compared with the placebo group (95). This reduction in PAI-1 has also been shown in non-diabetic, postmenopausal women (96). In another study using 143 participants from the Framingham Offspring Study (a long-term, prospective evaluation of risk factors of cardiovascular disease), levels of plasminogen activator inhibitor (PAI-1) antigen and tissue plasminogen activator antigen were measured. Fibrinolytic parameters for subjects with high estrogen status (premenopausal women and postmenopausal women receiving HRT) were compared with those for subjects with low estrogen status (men and postmenopausal women not on HRT). The results showed that the presence of estrogen, either naturally in premenopausal women or as a result of HRT in postmenopausal women, was associated with lower levels of PAI-1 and tPA antigen compared with those subjects expected to have low estrogen status (97). Other pharmacologic interventions that may modulate the fibrinolytic system include angiotensin-converting enzyme inhibitors and gemfibrozil (98, 99).

Conclusion

Coronary heart disease is the leading cause of morbidity and mortality in the United States. It affects both men and women. While women share many of the traditional risk factors with men, there are many significant differences (e.g., diabetes is a stronger risk factor in women than in men). New insights into the pathogenesis of atherogenesis underscore the fact that CHD is more than the consequence of arterial obstruction secondary to lipid deposition; it is an inflammatory process that occurs in response to endothelial dysfunction. As a result, "emerging" cardiovascular risk factors have been proposed. These include dyslipidemia, Lp(a), hyperhomocysteinemia, hypercoagulable states, and oxidative stress. Understanding these "emerging" risk factors has led to the development of new strategies to treat CHD. Gender differences are apparent in these "emerging" risk factors. For example, a high triglycerides level is a greater CHD risk factor in women than in men, especially those with diabetes, and decreased homocysteine level is associated with increased estrogen status. Women also have higher levels of fibrinogen, which has been associated with increased risk of CHD. Further investigations into gender differences will help influence the management of CHD in women and thus help prevent a disease that is the leading killer of women.

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Nocardiosis Presenting as an Anterior Mediastinal Mass in a Patient with Sarcoidosis

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Abstract

We report a patient with tissue-proven sarcoidosis receiving adrenocorticosteroid medication, who developed an enlarging mediastinal mass. Transcutaneous needle biopsy of the mass yielded pus which grew *Nocardia asteroides* on culture. Pleural effusion, bronchoesophageal fistula and brain nocardia metastases occurred. All evidence of active infection cleared with sulfa therapy. An enlarging mass in a patient with sarcoidosis unresponsive to corticosteroid therapy should provoke studies for other causes of mediastinal disease, including opportunistic infections.

Key Words: Nocardia, nocardiosis, sarcoidosis, prednisone, mediastinal mass.

Introduction

NOCARDIA ASTEROIDES is found in dust and soil. The lungs serve as the portal of entry, but resultant disease is relatively uncommon. While pulmonary infection is infrequent, opportunistic infection by *Nocardia* may spread from the lungs to other sites. Nocardiosis has been reported to complicate pulmonary alveolar proteinosis, malignancy, organ transplantation, corticosteroid therapy, and, rarely, sarcoidosis (1, 2). We report a patient with proven sarcoidosis receiving prednisone. She developed an enlarging anterior mediastinal mass originally thought to be growing sarcoidal mediastinal lymph nodes, but proved to be a nocardial mediastinal abscess with a bronchoesophageal fistula.

Case Presentation

In 1994, a 32-year-old white housewife complained of cough and dyspnea. A chest radiograph showed bilateral hilar lymph node enlargement and pulmonary infiltrations typical of radiographic stage 2 sarcoidosis. The patient was a housewife who had not traveled outside the New York metropolitan area. Diagnosis was made by bronchoscopic biopsy, which showed granulomas with negative smears and culture for acid-fast bacilli and fungi. Tuberculin skin test was negative. Following the administration of prednisone, she improved. She was well until January 1998, when she again developed dyspnea and a non-productive cough. Chest radiograph revealed an enlarging mediastinal mass thought to represent exacerbation of sarcoidal lymph nodes. Prednisone was increased from 5 mg to 60 mg/day. Despite this increase in corticosteroids, her symptoms worsened and she became febrile. She was hospitalized at The Mount Sinai Hospital on February 4, 1998. On admission, examination revealed that she was in acute respiratory distress. She displayed the following vital signs: temperature 38.1°C, heart rate 130/min, respiratory rate 26/min, and BP 130/80 mm Hg. There was dullness to percussion and decreased breath

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sounds over the right lower hemithorax. There were no murmurs, the liver and spleen were not enlarged, and there were no skin lesions or peripheral lymph node enlargement. The joints were normal. WBC was 29,000/mm^3 with 74% neutrophils. Chest radiogram revealed a large right mediastinal mass, a loculated right pleural effusion and bilateral interstitial infiltrates (Fig. 1). Thoracentesis showed an exudate with 22,000 WBC/mm^3. CT scan demonstrated an anterior mediastinal mass of fluid density (Fig. 2). A CT-guided biopsy of the mediastinal mass yielded purulent material. Preoperative bronchoscopy demonstrated a large endobronchial wall defect on the medial aspect of the left lower lobe bronchus (Fig. 3). The esophageal mucosa could be visualized through this defect. The bronchoesophageal fistula was confirmed by esophagoscopy. Intraoperative biopsy was negative for tumor.

Two days after admission, the patient underwent a limited, right-sided, transverse parasternal thoracotomy with drainage of the mediastinal abscess and empyema. This abscess was found to be contiguous with the pleural space inferiorly. Intraoperatively, an air leak was detected from the left lung. Chest tubes were placed to drain the abscess. Gram stains and stain for acid-fast bacilli were negative. Cultures of the mediastinal fluid ultimately revealed weakly positive, acid-fast, true branching rods, consistent with *Nocardia* (Fig. 4). On the tenth hospital day the patient was confused, and one week later she was somnolent without focal signs. Imaging studies of the brain revealed multiple cerebral abscesses (Fig. 5). No spinal tap was performed. Sulfonamide 1 gm q6h was initiated. A feeding gastrotomy was performed to place the esophagus at rest. A sinus tract connecting the mediastinal abscess and the small anterior thoracotomy wound developed postoperatively and was utilized to effect enhanced suction cleaning of the intrathoracic abscess and to decompress the cavity. The cultures of fluid draining from this sinus tract also grew out *Nocardia*.

Treatment with trimethoprimsulfamethoxazole (TMX) was started. No other surgical repair of the defects was attempted. Periodic bronchoscopy demonstrated gradual diminution of the bronchial defect and ultimate closure with no esophageal or bronchial abnormality. During the next 3^1/2 months the patient improved and was discharged receiving

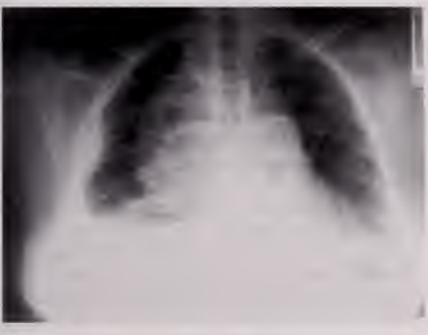

Fig. 1. Portable chest AP radiograph showing loculated right pleural effusion and large right mediastinal mass.

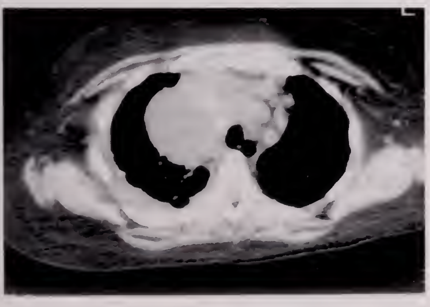

Fig. 2. CT scan of the thorax showing right mediastinal mass.

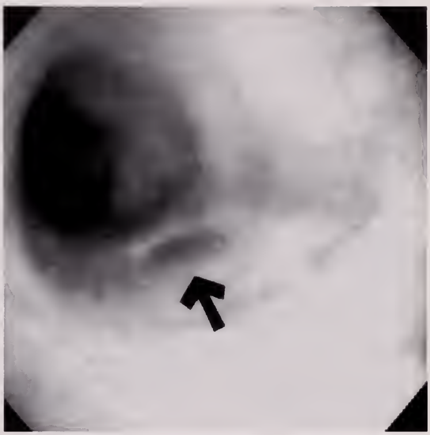

Fig. 3. Photograph taken at bronchoscopy showing a perforation of the medial wall of the left lower bronchus through which esophageal mucosa was visualized (arrow).

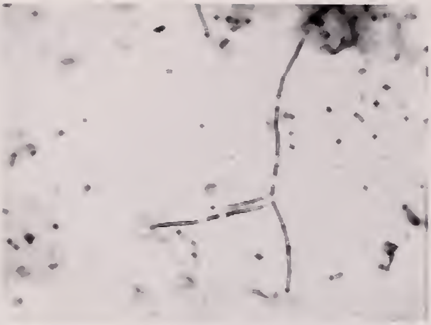

Fig. 4. Smear of *Nocardia* from mediastinal fluid. Weakly acid-fast, gram-positive branching rods seen in smear of aspirated mediastinal fluid. Similar organisms were seen in smears of pleural fluid and anterior thoracotomy wound. Magnification 1000x.

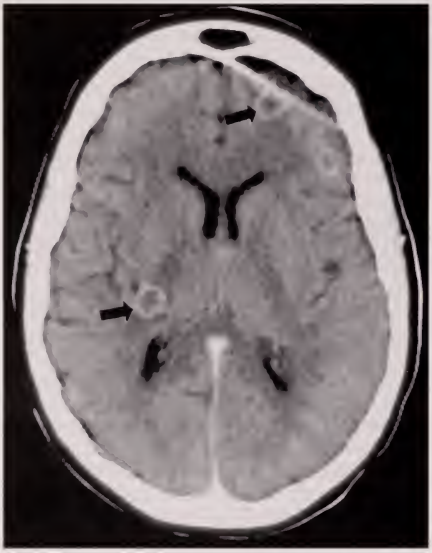

Fig. 5. CT scan of brain showing multiple abscesses consistent with *Nocardia* metastases (arrows).

oral TMX. Three months after discharge, she was eating normally, gaining weight and had returned to almost all activities. TMX therapy was continued for one year after surgery, by which time all signs of active infection had cleared and she had returned to her normal activities.

Discussion

In 1888, Nocard described actinomycetes in cattle in Guadaloupe (3). Eppinger first described "pseudo-tuberculosis" caused by similar aerobic branching organisms, which he referred to as *Nocardia* (4). Nocardiosis is caused by species of this genus, of the family Nocardiaceae. *N. asteroides* is the most common cause of human nocardiosis. Rarely, infection may result from ingested, contaminated food or by traumatic inoculation. *Actinomyces* infection is often confused with infection by *Nocardia*. Both organisms are filamentous, branching gram-positive rods that cause indolent, slowly progressive disease. *N. asteroides* is weakly acid-fast. *Actinomyces* is not acid-fast and is an anaerobic organism. "Sulfur granules" are rarely found in *Nocardia*, but are common in *Actinomyces*.

Inhalation of *N. asteroides* usually does not cause disease in immunocompetent hosts. *N. asteroides* infection most commonly occurs in immunocompromised hosts. Pulmonary nocardiosis is initiated by inhalation of *Nocardia* present in dust or soil. The disease starts in the lungs and may disseminate to other sites, most commonly the central nervous system, soft tissues and bone (1, 3). Between 1888 and 1960, 179 cases of nocardiosis were reported. None of these patients had sarcoidosis (5). *N. asteroides* has been reported in patients with pulmonary alveolar proteinosis, malignancy and organ transplantation, and in patients receiving corticosteroid therapy (1). Krick et al. reported *N. asteroides* infection in seven heart transplant patients in a 22-month period (6). All of these patients were receiving corticosteroids and azathioprine. In 1974, Beaman reported 198 patients with nocardial infection. Eighty-five percent of the patients had an underlying illness or were receiving immunosuppressive therapy (7). The diagnosis of sarcoidosis or corticosteroid therapy was not mentioned in these patients. Since sarcoidosis does not cause immunosuppression except when treated with corticosteroids, it is likely that corticosteroid treatment enhanced the risk for infection in our patient. There are four prior case reports of *Nocardia* in patients with sarcoidosis. Three of the patients were receiving corticosteroid therapy (2, 8, 9). The fourth patient had sarcoidosis and chronic granulomatous disease (CGD) and developed a cavity with *N. farcinica* (10). The immunological defect of CGD probably rendered the latter patient susceptible to the opportunistic infection.

Radiographically, nocardiosis may present as consolidation, well-circumscribed nodules, large, multiloculated abscesses or cavities (11). Extension of the infection to the pleura is common (11, 12). Bronchopleural fistulae have rarely been reported (13). There is only one previous report of nocardiosis presenting with an anterior mediastinal mass. In that patient, who did not have sarcoidosis, the lesion began as a subcutaneous mass that ruptured into the mediastinum (14).

The pathogenesis of the pleural and mediastinal purulent nocardial infection and bronchoesophageal fistula in our patient is speculative. It is possible that the involved areas were seeded due to lymphohematogenous spread of the infection, similar to the spread of the infection to the brain. Alternatively, the patient had a nocardial lung abscess which ruptured into the pleura and possibly the mediastinum. Involvement of the mediastinal lymph nodes, with rupture into the left main bronchus and esophagus, completes this scenario.

Patients with sarcoidosis receiving corticosteroids are susceptible to opportunistic infections, rarely nocardiosis. An enlarging mediastinal mass in a patient with sarcoidosis not responding to increased steroid medication, should evoke a complete differential diagnosis of mediastinal disease, including opportunistic infections.

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Issues in Medical Ethics

Understanding Professionalism and Its Implications for Medical Education

Rosamond Rhodes and Daniel A. Moros, guest editors

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Introduction

Daniel A. Moros, M.D.
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Issues in Medical Ethics: 2000

The concept of "professionalism," with its focus on the character as well as the behavior of physicians, has received increasing attention in medicine and in medical ethics. Physicians are turning to the concept of the "profession" as a potential institutional counterweight to the growing role of commercial, for-profit organizations within health care and the shifting priorities and regulations of government. In the 1990s, mention and discussion of professionalism snowballed into 655 journal articles. An additional 267 articles on the subject have appeared in just the past 20 months, including entire journal issues devoted to the subject and reports by professional associations (1–3).

This increasing attention to professionalism and the variety of ways that the concept is being used, sparked our concern about how well the concept was understood and how widely that understanding was shared. Because medical educators were beginning to address the importance of professionalism in medical education, it was obvious that they would need a clear grasp of the concept to guide their curricula and educational programs. To that end, we dedicated our fifteenth annual ethics conference to "Understanding Professionalism and Its Implications for Medical Education." It was held at the Mount Sinai School of Medicine in New York City on November 3, 2000. The speakers and panelists included physicians, sociologists, historians, philosophers, lawyers, educators, a medical student, and a medical resident. The participants were Bernard H. Baumrin, Ph.D., J.D., *professor of philosophy, the Graduate School, CUNY, adjunct professor of medical education, Mount Sinai School of Medicine;* Alex Stagnaro-Green, M.D., *dean for student affairs and medical education, Mount Sinai School of Medicine*; Rosemary Stevens, Ph.D., *professor, history and sociology of science, University of Pennsylvania*; Thomas Rüten, P.D., Dr., *Institut für Theorie und Geschichte der Medizin, University of Münster, Germany*; Steven R. Latham, J.D., Ph.D., *director, Center for Health Law and Policy, Quinnipiac College School of Law*; Haavi E. Morreim Ph.D., *professor, medical ethics, University of Tennessee College of Medicine*; Edmund D. Pellegrino, M.D., *John Carroll professor of medicine and medical ethics, Center for Clinical Bioethics, Georgetown University Medical Center;* Daniel A. Moros, M.D., *associate professor of neurology, Mount Sinai School of Medicine*; Fred Hafferty, Ph.D., *professor of behavioral sciences, University of Duluth School of Medicine;* Samuel Bloom, Ph.D., *professor of community and preventive medicine, Mount Sinai School of Medicine;* Mark Siegler, M.D., *Lindy Bergman distinguished service professor of medicine and director, MacLean Center for Clinical Medical Ethics, University of Chicago*; David M. Nierman, M.D., *clinical associate professor of medicine and director, Medical Intensive Care Unit, Mount Sinai School of Medicine*; Roger Cornwall, M.D., *PGY IV, Department of Orthopaedics, Mount Sinai School of Medicine;* Jennifer Fehser, *fourth-year student, Mount Sinai School of Medicine;* and Arthur Rubenstein, M.B.B.Ch., *dean, Mount Sinai School of Medicine.*

The historical and sociological presentations by Rosemary Stevens, Thomas Rüten, and Steven Latham made it clear that, regardless of the personal reasons one has for choosing to become a doctor, making that choice essentially involves undertaking specific moral responsibilities. Medicine is seen as a profession and its unique professional commitments have been recognized, accepted, and endorsed throughout its history. Societies have acknowledged medicine's special expertise, authorized its special powers and privileges, and relied upon its special obligations to be concerned with the patient's well-being and serve the members of the society. Understanding medicine as a profession explains its ethics in terms of the profession's unique position in a society.

Competence, caring, and trustworthiness define the core content of medicine's professional responsibilities. These ideas were repeatedly expressed by conference participants. Professionalism requires physicians to be knowledgeable and skilled, and to continuously update their expertise and proficiency. Professionalism demands that physicians suppress self-interest, in the service of the well-being of their patients. Professionalism entails that physicians make themselves into the kinds of people who will be trusted by society and who will be worthy of that trust. And it demands that the institutions of medicine be designed to promote society's trust and not undermine it.

From the presentations, it also became clear that a conception of medicine as a profession defines the medical team as a group of professionals (e.g., physicians, nurses, physician assistants, social workers, nutritionists, patient representatives, physical and occupational therapists) with a shared core of common professional duties. All members have the ethical responsibility to be aware of and responsive to their colleagues' professional duties and to be caring and respectful in their professional interaction with each other. The values and commitments that guide team-based medical decision making must be transparent to patients and the community, because they must be the commitments and values of medical professionalism.

From this perspective, medical ethics can be seen as the sum of moral commitments of all health care professionals. It can be discussed from the perspective of the character, or virtues, that a medical professional must have, as Dr. Pellegrino does. Or it can be discussed from the perspective of what a physician needs to understand and do, as Dr. Siegler does. Unfortunately, features of the prevailing medical environment, current social practices, and contemporary legal decisions can impede or undermine professional behavior, as Drs. Morreim, Hafferty, and Bloom explain.

The conceptual understanding of "professionalism" has obvious implications for the education of society's future doctors. Medical education should, of course, promote professional competency. The educational process should also promote the development of the essential habits of disposition and attitude to perform as a good physician should, that is, the character (i.e., virtues) of a good physician. In other words, as a part of medical education, medical ethics education should primarily be concerned with inculcating medical professionalism. This involves helping students to understand the content and the justification of their special responsibilities as physicians as well as to accept their professional responsibilities as important and overriding. Medical education has to pay serious attention to these aspects of physician training. We have to help our students to understand their professional responsibilities, to be people who have the requisite character, and enable them to do the right thing as the well-formed professional would do it. That is the essence of professionalism.

Regrettably, as Drs. Nierman, Cornwall, and Jennifer Fehser explain, medical education does not always meet its mark. The proceedings of this conference provide insight into areas that require significant attention and commitment from medical educators. The formal and informal curricula of academic medicine must convey to our students that being a doctor is, in a sense, a lifelong commitment to medical professionalism.

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Welcome

ALEX STAGNARO-GREEN, M.D.

THE EXISTENCE OF THIS CONFERENCE and the extensive medical ethics program of the Mount Sinai School of Medicine led by Dr. Rosamond Rhodes are an indication of the critical role that medical ethics plays at Mount Sinai as an institution and in medical education in particular. In this issue, different perspectives on professionalism, including the history of professionalism, professional responsibilities, education and professionalism, and the perspective of teachers and faculty are analyzed.

I would like to add one other perspective, that of the patient. Following a physician strike in Ontario in 1987 the Canadian government polled the country to determine what outcome Canadian citizens wanted from their medical schools. That exercise, the CanMeds 2000 Project, identified professionalism as one of the five most important qualities of being a physician. Similarly, but not surprisingly, the Accrediting Council of Graduate Medical Education in the United States also highlighted professionalism as one of its five major goals.

In preparation for this conference I asked three of my patients for their definitions of professionalism. These were patients whom I have known for a long time and who have very different personalities and illnesses. The first said, "Technical expertise is expected. Professionalism has to do with character. It's efficiency and a minimum of fluff. Doctors should not be unduly trying to impress." The second patient commented, "It's a nice personality, patience and follow-up. Accessibility is critical." He then stopped and thought for a long time before continuing. "The doctor making that extra phone call, that extra effort, that's what professionalism is all about." And the last patient said, "Professionalism is critical. It's a good bedside manner. It's empathy, a total interest in the patient, including the medical, social and psychological aspects of that person. It's the way the doctor speaks to the patient." This person also paused, stared at his fingers and then went on. "First impression is very important. The doctor must be well groomed and the fingernails must be clean," at which point I quickly glanced at my nails.

What I learned from my patients is that they all have very different definitions of what professionalism is, but they all felt that it was at the core of being a doctor. Their remarks highlight the importance of these proceedings.

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Presented at the Issues in Medical Ethics 2000 Conference at the Mount Sinai School of Medicine, New York, NY on November 3, 2000.

Key Words: Professionalism.

Themes in the History of Medical Professionalism

ROSEMARY A. STEVENS, PH.D., M.P.H.

Abstract

Professionalism in medicine is an ambiguous term. Discussions are hampered by understandings of the past that are counterproductive to today's debates. Three decades of criticism of physicians as self-interested and arrogant, and of professional organizations as unfairly monopolistic have shaken the confidence of professional leaders and their constituents in their ability to act as a positive social force, and left the concept of professional autonomy without a useful meaning. Inherited assumptions about conflict between the profession, government and the market have encouraged organizational policies to fight familiar enemies for short-term gains, rather than reinvent professionalism as a social force or seek new strategic alliances. This article stresses the importance of distancing the present from the past in re-inventing professionalism for the future, and lists eight fundamental goals.

Key Words: Profession, professionalism, history, trends.

PROFESSIONALISM IN MEDICINE can be viewed through many different lenses, for over the years the word "professionalism" has taken on many different loaded meanings. The very fact that this article is part of a journal issue of presentations suggests that the term is ambiguous at best — that there are virtues that need to be taught, practices that need to be better understood, and warnings that need to be heeded about the dangers of personal corruption in an unsteady, if not evil, marketplace. Professionalism, it seems, can no longer be taken for granted as a core of behavioral expectations that are inherent in becoming a physician. Similarly, on the wider social stage professionalism is no longer assumed to mean unmonitored professional self-government, nor can it be assumed to reside in trusted professional institutions (including medical schools) that work unequivocally for the public good.

How did the American medical profession get to this point of confusion and ambiguity? And more to the point, what should be done about it? The purpose of this paper is to place our contemporary discussions of the larger social roles of the medical profession in historical perspective. I will focus on two themes critical to the development of professionalism's next steps. The first theme is that it is urgent to revise the received wisdom that says the medical profession is in decline. I will suggest that dominant explanations of the history of the medical profession during the past century have shaped public and professional attitudes in ways that are restrictive and unhelpful. However, attitudes can — and should — be changed. This is an enormously important time to be recreating professionalism in medicine, because the profession may be at a critical break in its history.

Second, there is much more to be said about the fundamental relationships between the medical profession, government, and health care system as they have evolved in the United States. The first theme, on historical explanations, is perceptual; the second, on alliances, is strategic. I will discuss each in turn and end with a brief conclusion. My conclusion is that the way for the medical profession to become

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The author was a recipient of a Robert Wood Johnson Investigator Award in Health Policy Research.

more ethical — more truly "professional" — in this century is for the profession and its leadership to finally come together and insist on the highest professional standards, as we move toward universal, national health benefits, regardless of whether these are provided by private or public agents. The medical profession must control the standards of care; otherwise, we may be heading toward an unacceptable mediocrity.

Interpretations of the Past: The Ongoing History of Professionalism

As we all know, professionalism as a concept is context-dependent; we are all creatures of our environment. The historical environment of this meeting is more than thirty years of critiques of the medical profession. These critiques have focused on physicians as self-interested individuals who have masqueraded for too long as aloof, scientific altruists, and have behaved, collectively, as a questionable cultural force in the United States.

Whatever one may think of the status of medicine today, thirty years ago this status was met with outrage and verbal attack, chiefly from those outside the profession. Philosopher Ivan Illich (1) described medicine as a conspiracy against the public. Psychiatrist Thomas Szasz (2) was widely quoted as describing his own field as pseudoscience, and as denying the existence of mental illness. More measured scholarly attacks were similarly devastating to the high morale and sense of self-entitlement of those within the profession in the 1950s and 1960s. Sociologist Eliot Freidson (3) observed in a major study in 1970 that American physicians exerted an unreasonable level of social control. Freidson criticized the medical profession for its "splendid isolation" from society at large, an isolation that provided it with a "protected insularity" that could work against the public interest. Through this insularity, he suggested, the profession could bask in a "self-deceiving view of the objectivity and reliability of knowledge and the virtues of its members." Through this insularity physicians could flaunt a "mistaken arrogance" about their social roles and missions.

To some extent the medical profession had been oversold (or had oversold itself) by the late 1960s. Reaction had set in. The runaway costs of health care and the failure of the Great Society programs of the 1960s to cover the entire population with effective health services were joined by widespread recognition of the limitations of modern medicine, particularly in dealing with chronic diseases. At the same time, there was a growing tendency to see doctors, as well as other professionals, as being no different from the operators of any other business. In the 1970s, the Federal Trade Commission began looking closely at medical schools, accrediting procedures and professional associations and saw them as conspiracies designed to restrict the number of physicians, and thus as sinister actors who restrained competition unfairly in order to lock in high medical fees. The glory days of professional autonomy seemed to be coming to an end.

With this perception of, at best, disappointment, and at worst, betrayal of the American public by a venal profession, came a sense of loss (and anger) that still lingers on within the profession in its attitudes and actions. As one physician remarked at a recent meeting I attended, "If we have always been self-interested historically as a profession, how do we know we are not being self-interested today?" Without clear ethical guidelines of what the profession should stand for in the present, how can one move ahead with the necessary confidence to push for professional and social change in the future?

The let-down of professionalism in the 1970s and 1980s seemed cataclysmic for two reasons. First, there was the myth of sudden change from an autonomous, publicly respected profession to one vilified in the public press. Second, there appeared to be potent rivals for the authority that American physicians thought they owned. Looking back from the early 1980s, historian John Burnham (4) described the first sixty years of the twentieth century as "American medicine's golden age." He, like others, asked what had happened since. Sociologist Paul Starr (5), publishing at the same time, widened the scope of the medical critique to take into account the growing privatization or monetarization of medicine. He depicted a history of a "sovereign profession" (a powerful term with un-American connotations) that once had reigned supreme, but now was threatened by the "coming of the corporation." In a more anxious mode, Arnold Relman (6), editor of the *New England Journal of Medicine*, warned, on behalf of patients, against the "new medical-industrial complex" as inimical to the free exercise of professional responsibilities.

All of the criticisms seem to come together in one powerful myth of rise and fall, where professionalism had been (on top), and where it was going (downhill). The message was resolutely downbeat. Doctors, once heroes, even kings, had fallen from the pedestal of public adulation. Like the members of other professions in the United States over the past 30 years, doctors could no longer play the role of unexamined cultural hero.

The situation was painfully bad for physicians because the American medical profession had to face more stress than other American professions. Unlike law or architecture, which were also subject to social criticism, the medical profession during the 1980s was challenged simultaneously by massive destabilization in the environment of medical practice. The roots of the present malaise in medical professionalism include the rapid growth of managed care in the late 1980s and the growth of its influence in the 1990s. But beyond this, the roots of today's malaise within the medical profession have to include the political choice in the United States not to have a high standard of care, assuring both patient and professional dignity, through the mechanism of national health insurance or other forms of national governmental guarantees for health care. Such possibilities were not policy alternatives for other American professions; for example, no one was suggesting national insurance for architects or lawyers.

But beyond this, far more than is true for other professions, medicine has long been the stuff of myth. Thus, there was a ready ground to accept the myth of rise and fall. Medicine occupies the imaginative land of childbirth, of life and death, of individuals fighting their own battles against disease, and of biomedical scientists struggling toward "truth." Not surprisingly, then, the recent history of the medical profession has often taken on the character of an American morality tale, with the profession as victim of its own hubris. Myths are powerful, formulaic ways of thinking about power in any culture, and it has been difficult not to think of professionalism in these terms. Thus, the American medical profession has (apparently) fallen from grace since the 1970s, overcome by the "market," whose proxy from the late 1980s was managed care corporations. A great profession had arisen to its golden age in the mid-20th century; it was conquered by a new hero; and is apparently slipping to subservience, if not oblivion.

For the American medical profession, largely unprotected by government, the message of gloom, doom, and failure had two striking components by the 1990s. On the one hand were the very real forces of managed care, which gained power in the 1990s through controlling the flow of insurance payments. On the other was a powerful narrative of the failure of professions that drew on powerful cultural myths of heroes and villains, rise and fall, and conflict. This narrative was particularly piquant for American medicine, which had risen so high in cultural esteem by 1960 and had sunk so low by the 1990s. By the mid-1990s it seemed reasonable to interpret the ongoing history of medical professionalism in the United States as a battle among competing cultural forces: the market, government, and professional guilds, with the last one having lost out. Sociologist Elliott Krause (7), noting declines in the cultural power of professional guilds cross-nationally (and across professions), singled out American medicine as a special (mythic) case by calling his section on the American medical profession, "Fall of a Giant."

Today both this interpretation and the rhetoric in which it is couched are decades overdue for reappraisal. The pressures on the medical profession by the 1970s were much more complex than simple explanations might suggest. In complex, bureaucratic societies such as ours, with multiple professions typically based in organizational settings, the guild paternalism of old-style professions such as medicine, theology, and law had clearly outlived its usefulness by the 1970s. But that did not necessarily: (a) predetermine a decline in the moral authority of the profession in American culture, or (b) preclude a rise in the policy influence of the profession within health care organizations. In choosing not to have universal national health insurance in the United States, as is the case in other technologically sophisticated nations, Congress (and thus the American people) effectively left the profession out on a limb, to be picked over by creative corporations. Obviously, more than universality is required for the highest level of professionalism, for unless thoughtfully implemented, universality can lead to demoralization and a low common standard denominator of care, with the delays, and lack of equipment, technology, urgency and initiative seen in some other systems. In promoting both access and quality, effective medical leadership is vital to the future of health care in the United States.

Professions, Corporations, and Government

Under managed care the medical profession has not been able (or willing) to exercise professionalism through acting effectively as the sole advocate for maintaining excellence in the quality of care. Who then are medicine's natural allies? In Europe it is much clearer than it is in the United States that doctors and states are in "mutual dependence"; that political acceptance of universal health coverage has consolidated the position of the medical profession; and that today's doctors have a voice within the health system, rather than in opposition to it, as is the case in the United States (8). (However, having a voice does not necessarily mean that voice is used effectively, either for patients or for the profession). In the United States the history of professionalism has isolated the medical profession into a separate domain, distinct from both government and the market. This is not a helpful way of rethinking professionalism at the beginning of the 21st century, in the context of complex systems, corporate organization, and pervasive government regulation. In the realm of market versus profession, American medicine is struggling today with the need to reconcile old ideas with new experiences — but the old rhetoric of conflict keeps getting in the way. Similarly, the profession's long opposition to government intervention into medicine gets in the way of seeing federal and state governments as its natural allies in the future.

Just as the profession has been powerfully influenced by moral narratives of its rise and fall in the 20th century, so too it bought into the American doctrine that professions, corporations and government occupy separate, competing social spheres. The idea that professions and commerce are in direct opposition, in its current iteration of the medical profession versus managed care, is a holdover from early 20th century rhetoric. For the professions, developing at the same time as the emerging industrial state (actually as part of it), it was as if there were two, mutually dependent social worlds: the selfish, messy, dirty, pragmatic world of commerce, and the selfless, ordered, clean, idealistic worlds of charity and science occupied by the professions. Actually, it was apparent to observers even in the 1920s that the lines were not so clear. Professions have always operated in their own marketplace, selling their services to clients or patients. Moreover, even in the early 20th century, at least some medical specialists chose their fields based primarily on financial gain, not altruism. Nevertheless, the ideology was useful in carving out a high cultural profile for medical professionalism as an altruistic enterprise. The ideology became invaluable as a justification for professional policies that maintained the autonomy of professionalism in medicine, and fought any threats of commercial intervention.

For many years AMA policy and politics overtly sanctioned the role of the medical profession as a source of idealism in the market. Physicians were forbidden to advertise on the grounds that this was unprofessional. Similarly, the perceived threats of contracts for service and corporate forms of practice assumed that the ideal professional role would be compromised if professional services were at the disposal of an organization. In practical terms, the conceptual division of a selfish market on one side and an idealistic profession on the other became less and less tenable as it became common for doctors to work in groups as professional corporations, as health insurance proliferated after World War II and as Medicare stimulated market-like behavior in hospitals across the United States. Nevertheless, even though the environment of medical practice changed radically during the 20th century, the idea of the market as the enemy of the medical profession continued, reappearing with force in the 1980s and 1990s as the expression of hostility to managed care. The most common professional response to managed care has been conflict rather than partnership. There has been an awkward disconnect between physicians and the managers of managed care. Yet discussions of modern professionalism cannot avoid questions about the proper exercise of medical responsibility in networks, teams and systems, the ethical standards of organizations, and the behavior of individuals.

Similar comments can also be made about the profession's past isolation from government in areas of most concern to patients, notably, access to appropriate, high-quality care when needed, without insurance, class, or geographic barriers. The history of the American medical profession has been marked by hostility to potential interference from government (notably via proposals for universal health insurance) over the years, and such views have corresponded with strong anti-government political views by many members of the population. There has been some justification for such views as it concerns the VA system, Medicare and Medicaid. Universality for these populations has been accompanied by conflicts and political decisions that are not always in the best interests of patients or doctors. Yet the medical voice has been surprisingly quiet.

Supported by the general population, the profession was able to maintain a delicate balance as a supposedly independent force, outside of government and the market for much of the last century. This stance allowed the United States to avoid the path of relatively strong governmental control over health policy that was taken by many other nations, sometimes with success, sometimes with failure. Such apparent independence had unexpected consequences for the profession, because it seemed that the profession was naturally autonomous or privileged in American culture, rather than existing to serve broader political and social goals. The profession has reached this point in its history with shattered assumptions about its autonomy, and a tendency to fight short-term battles rather than seek long-term goals. As managed care evolves in one form or another, and as we move toward universality, the profession must take control of standards or it may meet the fate of schoolteachers and social workers. Frequently, these noble warriors are forced to meet the lowest standard rather than a reasonable, let alone highest, standard (9).

Conclusions

Today the environment of professionalism has shifted to such an extent that the social meaning of medicine as a profession has to be renegotiated, and the rhetoric shifted away from one of conflict, represented by the dichotomy of market and professions, or professions and government. The great pleasure of talking about professionalism today, rather than in 1970, 1990, or even 1920, is that it is much easier today to jettison old ideas. The inherited history of professionalism, with its assumptions about a profession that is (a) in decline, and (b) in necessary conflict with market and government, is clearly not helpful to thinking about professionalism in medicine today.

The American medical profession has a choice today of what to do about past perceptions. This is more than an idle observation. Such a choice has practical consequences. If it is generally believed that medicine is oppressed and in decline, then behavior such as harassment of doctors by insurers, or fudging (lying) on patient diagnoses for insurance coverage, becomes legitimized (perhaps even justified) as part of a more general pattern of pessimism and complaint. A dismal present is compared with a more glorious past. Similarly, if decline seems preordained and continuous, the potential collapse of the nation's medical schools seems more than likely. On the other hand, if it is assumed that what goes down may come up again, or that attitudes toward health policy tend to run in cycles, the future of professionalism is not so bleak. One might even be optimistic. All of which is to say that assumptions about history affect the way we all behave.

Physicians, as members of our society, are naturally influenced by its messages. In the last few years managed care has become a generic public villain, thus supporting a hostile attitude toward it by organized medicine. "Health policy is easy territory for demagogues" proclaimed a recent editorial in *The Washington Post*, castigating both major presidential candidates for "indiscriminate HMO-bashing rhetoric" that would make solutions to real problems harder to achieve (10).

What kind of environment is conducive for physicians to be ethical in today's health care environment? The following partial list emphasizes the fact that the fundamental issues lie in how health care is organized, regardless of who is in control of it:

1. The ability to treat patients, using high standards of care, without undue concern about cost and insurance issues as these affect individual patients.
2. Satisfaction in providing continuity of care to patients.
3. Building and maintaining trusting relationships with patients and with the general public.
4. Opportunities to participate creatively in improving the network or system on behalf of patients.
5. Good information systems for more effective patient care and continuous improvement in clinical and team skills.
6. The ability to exercise professional curiosity (most formally, through clinical research and evaluation).
7. Open and fair communications with other members of the health care organization, including managers.
8. Reasonable working conditions and income levels.

Since ethical principles are difficult to maintain in a corrupting environment, professionalism in this century demands a major professional commitment to establishing and maintaining ethical principles in the environment of medicine. At the very least, this means overt recognition of the delegated role of professions as agents of the highest goals of the state or culture, and the importance of universal access to medical care as an ethical goal for the profession. The route to professionalism in our time is to have national health care, responsive to the public; its rules transparent; its universalism consolidating the public roles of the profession; and a profession that is well-organized, canny, and an effective fighter for, and guarantor of standards. The responsibilities of professionalism today are awesome. Can the profession overcome the burdens of its received history? Are professional organizations competent and ready to move ahead?

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Medical Professionalism:

A Parsonian View

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Abstract

This paper argues for a normative conception of medical professionalism based on the work of sociologist Talcott Parsons. Such a conception grounds medical professionalism on the expert authority of the physician; the concept of "authority" is therefore discussed at length. Parsons' view also lays much stress on the fact that the proper exercise of medical authority nearly always involves aligning the interests of individual patients with those of society at large. Parsonian professionalism looks to professional institutions such as medical schools, societies and journals to secure the competence and ethical behavior of professionals, and to help ensure that professionals' exercise of authority is never biased by private financial interests or by public political power. Professional institutions should encourage professionals to develop a set of preferences and desires (e.g., for respect of their peers, and not for power or financial gain) that will tend to make them trustworthy authorities.

Key Words: Professionalism, medical profession, authority, patient and society, Talcott Parsons.

THERE IS ONE WAY of describing professions — a way that became current in the sociological literature of the mid-1900s — which we might term the "checklist" method. This method identifies an occupation as a profession if:

- Participation in it requires formal education;
- Its members enjoy control over their own occupational training standards and their own disciplinary mechanisms;
- There is a scholarly journal devoted to its standards;
- Its practitioners enjoy relatively high social status;
- Its practitioners have secured protection from state regulation as well as from market pressures; and so on.

The checklist method permits and even encourages ongoing debate about whether certain occupations "count" as professional, e.g., librarianship, social work and journalism. It also allows for speculation about the ability of occupations to acquire social status by "professionalizing" themselves through the acquisition of the various items on the checklist (1).

This checklist approach has some decided peculiarities. First, it gives ontological priority to occupational groups rather than to particular practices. It is professional groups or associations, after all, that can issue educational standards, publish journals, and so on. The checklist approach holds, in other words, that the title "profession" attaches not to particular kinds of work, but to a particular kind of social organization of work; that a professional association is not a union of persons who were, antecedently, professionals, but instead that persons can be professionals only insofar as they belong to professional associations. The second peculiarity of the checklist approach is that it describes professions in purely positive terms, when our ordinary uses of the word — "He's a real professional. She did a professional job. This isn't just my job, it's my profession" — have a decidedly normative cast.

As a matter of history-of-sociology, the checklist approach was the tail-end contribution

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of the structural/functionalist school of sociological thought about the professions — a school named for its belief that the structures of social institutions could be explained by the social functions they served. The founder of that school was Talcott Parsons — a man whose work dominated 20th century sociology in a way nearly unparalleled in any other field. (We might compare him to Noam Chomsky in linguistics.) In what follows, I propose that we re-introduce ourselves to the original Parsonian conception of a profession — a conception which gives ontological pride of place not to groups, but to the important work done by those groups' members, and which describes professionalism not just in organizational, but in moral, terms.

Parsons was not only a sociologist, but also a translator — the first person to translate Max Weber's monumental works of sociology into English (2). And it was in the course of his translation of Weber that Parsons' attention was first turned to the professions. He was working through Weber's discussion of the types of legitimate authority. One's authority, in Weber's view, was essentially the probability that one's commands would be obeyed. Weber located three varieties of legitimate authority: legal authority, in which people obey your commands because they recognize the legal legitimacy of your having issued them; traditional authority, in which people obey your commands because they have always done so; and charismatic authority, in which people obey your commands because something in your personality emotionally compels their obedience (3).

Parsons worried over this typology; he felt that Weber had missed a fourth, and important, variety of legitimate authority. This was expert authority: people obey your commands because they believe that you know something they don't know. This kind of authority Parsons explicitly associated with professionals.

In later essays, Parsons expanded upon the role of professional authority in maintaining modern society (4–6). Professionals, Parsons believed, were essentially double-agents or, if you prefer, "interstitial go-betweens." Their job was to use their authority to mediate between individuals — their clients — and society as a whole. Part of the time, they used their authority to curb their own clients' deviance — to align their clients' interests and actions with broad social norms. In this vein, we may think of the lawyer who scolds his corporate client into obeying environmental regulations, or the doctor who works to heal his patient in order that he might return to work and to his other social obligations. In each case, the "deviant" client is "mainstreamed" through the intercession of the professional. On the other hand, professional authority is sometimes used to create safety zones for individuals against the demands of social norms. Examples of this include the lawyer who goes to court to defend his client's unconventional religious practices, or the physician who writes a note excusing his sick patient from having to go to work. Professionals, in Parsons' view, are therefore constantly invoking their authority to negotiate and re-negotiate the normative boundaries between individuals and society.

Now, this project of interstitial negotiation can be successful — and in Parsons' view, has been successful — only when professionals maintain a certain outlook. Professionals, Parsons thought, must not be too strongly motivated by the desire for power, lest they attempt to achieve it by promoting social norms at the expense of individual liberty. On the other hand, they must not be too strongly motivated by profit, lest they allow their authority to be bought out by wealthy private clients seeking exemption from social norms. Instead, Parsons concluded, the professional project is successful only because professionals are motivated primarily by the desire for status and reputation — both among their peers and in society at large — rather than by the desire for money or power.

And it is because professionals are thus motivated that professional institutions — societies and university departments, publications and clubs — emerge as powerful socializers of professionals. It is not the existence of those institutions that first marks the professional as professional; they appear after the professionals do. But the existence of such institutions, by encouraging peer review and offering opportunities for professionals to compete for respect among themselves and before the public, does help assure that professional authority is exercised for the social good, in a way that keeps individual and community interests in proper balance. The "pro-fession" of professionalism — its "speaking forth" — thus occurs in the public articulation by and through professional institutions of the profession's standards, both technical and moral. Importantly, these standards, though they may be articulated by the profession through its institutions, are not simply the profession's private property — not, as it were, Masonic mysteries. In order both to properly socialize professionals and to inspire the public's trust and respect, the profession's standards of competence and ethicality must be fully acceptable and to a large extent be transparent to the public.

Here, then, are the core elements of a Parsonian profession: a profession is an occupation that uses its legitimate expert authority to mediate between individuals and society. (Here we can take a page from Kant (7), and note that physicians mediate between physical man and his society; lawyers between civil man and his society; and clergy between spiritual man and his society.) A profession's members are characteristically peer-oriented and status hungry, but not profit-motivated and not motivated by desire for political power. Their professional institutions socialize them for proper service in their interstitial role, and give them the opportunity for acts of profession before one another and society at large. These acts of profession both socialize the professionals and inspire trust from the public, facilitating the safe exercise of professional authority.

The Parsonian model of professionalism was torn apart by critical scholarship in the 1960s and 1970s. Critics argued — persuasively, I think — that the Parsonian view had ignored the exploitative actions of professional monopolists, who were in fact hungry not merely for status but also for both money and power; and, moreover, that it had ignored the actual failure of professional institutions to guarantee the quality of their members' work (8, 9). Finally, critics of the medical profession have pointed out that even physicians' expert authority is something of a sham: much medical practice is not based on scientific evidence, is not as uniform as truly scientific practice ought to be, and is heavily influenced by economic and marketing forces (10).

Nonetheless, even if the Parsonian model fails as a factual description of medical professionalism in America, I believe that there is much to recommend it as a normative description of what American medical professionalism ought to look like. Let us take a closer look at each of its elements to see why. I shall begin with a closer look at the nature of professional authority, and then make brief comments about the interstitial role of professionals, their motivations according to the Parsonian model, and their acts of profession.

The Authority of the Medical Profession

At the base of the Parsonian view is the idea that the authority of professionals is grounded in their knowledge and expertise. Our inquiry will be more precise if we pause for a moment to consider, more carefully, just what we mean when we speak of the professional's authority. Consider the following preliminary definition: One has authority if one's statements give others new and sufficient reason for holding a belief or taking an action.

Understanding the full import of this definition requires us first to note the two-fold distinction of authority on the one hand from force, and on the other from persuasion. According to Hannah Arendt, that two-fold distinction goes back to the origins of the concept of authority in Plato's writings. Plato, Arendt asserts, wanted to establish a form of rule in the polis which was "an alternative to the common Greek way of handling domestic affairs, which was persuasion, as well as to the common way of handling foreign affairs, which was force and violence" (11). Authority's hallmark, she notes, is "unquestioning recognition by those who are asked to obey; neither coercion nor persuasion is needed. (A father can lose his authority either by beating his child or by starting to argue with him, that is, either by behaving to him like a tyrant or by treating him as an equal.) (12). Authority thus requires some recognition by its subject that the person to whom the subject submits is entitled to obedience without having to procure that obedience by argument (13, 14). The obedience required by authority nonetheless remains "an obedience in which men retain their freedom" (11); one obeys authority not because one is forced to, but because one believes one has reason to (15).

This distinction of authority from power is by now a staple of Western political thought. "*Cum potestas in populo auctoritas in senatu sit*," wrote Cicero; "While power resides in the people, authority rests with the Senate" (11). Montesquieu thought of the judicial branch as the highest authority in constitutional governments, yet described its power as "somehow nil;" Mommsen referred to authority as "more than advice and less than a command, an advice which one may not safely ignore" (11). The Spartan ephors spoke with authority but were utterly powerless; their example inspired Rousseau to include in his *Social Contract* a group of wise men who could make authoritative pronouncements, but could not force compliance with them (16). Pierre Clastres has given us a striking example of separation of power from authority even outside the Western tradition: in certain South American tribes chieftains are responsible for giving daily speeches on the tribal law but are incapable of enforcing them (17). To move to a more familiar local example, the AMA's *Code of Medical Ethics* is developed by a Council of the AMA who have abdicated their seats in the AMA's House of Delegates, and who are powerless to enforce its requirements upon rank and file physicians.

The idea of separation of authority from persuasion is also quite familiar. It is perhaps most familiar in the context of parental authority; indeed, the all-too-familiar parental response, "Because I say so!" precisely asserts a reason grounded neither on coercion nor on persuasion. Business managers set employees to tasks without having to persuade them of their usefulness. Judges — especially trial judges — often make authoritative pronouncements without backing them up with reasons.

The application of this two-fold distinction to professional practices is fairly straightforward. My physician does not need to persuade me to take my medicine; and he is not at liberty to force me to take it. He tells me to take it twice a day with meals, and I do. It is similar with my attorney's advice about how best to draft a contract. He does not bully me into accepting his draft, nor does he take the time to persuade me, clause by clause, that I ought to accept it. I accept it on his authority. To demand explanations from my physician or my attorney would thus be to challenge their authority — to imply, perhaps, that they were overreaching that authority, or to question their competence as authorities. But we are getting ahead of ourselves. Thus far we have established only that a professional's authority allows her to secure our actions or beliefs without use of coercion, and without persuasion. But in virtue of what does her authority do this? And what, if anything, makes professionals' exercise of their authority normatively legitimate? Why ought anyone to accept the bare statement of another as a reason for belief or for action?

We can find a clue to the answer in the etymology of the word. The word "authority" comes to us from two different Latin words, *auctoritas* and *auctor*. *Auctoritas*, a legal term, referred to "a surety in a transaction, the testimony of a witness, or the means for the verification of some fact, for example, a document. It apparently then came to mean the respect or dignity or weight attached to the person or document involved" (13). *Auctor* (derived from the verb *augere*, "to augment, increase, enrich, tell about"), like "author," referred either to one who brings about the existence of something (as in "the author of the action"), or to one who "promotes the increase or prosperity of it . . . or by his efforts gives greater permanence or continuance to it" — as, for example, by writing it down or "giv[ing] an account of" it. In Roman political thought, the greatest example of an *auctor* was Romulus, founder of Rome; later "authorities" in Rome augmented or bore witness to his founding act.

Auctor, then, can generally be understood to refer to a founder or author, to whom a line of action can be traced back as the source; or to one who "augments" or "enriches" such a founding act; or to one who bears witness to or gives an account of such a foundation. These senses of *auctor* are, as Friedman points out, nicely summarized in the following passage from Gladstone (13):

> The proper idea is that of one who adds. In strictness, this must be adding to what existed before, as a witness adds to the thing his testimony about the thing. . . . From this original form the meaning passes on to a gradual creation, the creation of something that receives successive increment. . . . An "author" comes between us and the facts or ideas, and adds to them a . . . ground of belief, in his own assurance to us respecting them. . . . And hence perhaps we obtain the largest and clearest idea of "authority," as that which comes between us and an object, and in relation to us adds something to the object which is extrinsic to it, which is apart from any examination of it by ourselves, but which forms a motive . . . for belief or action. . . .

An authority in this sense is "an intermediary between the thing he is an authority on and the persons who accept him as an authority on that thing. He has access to it and they have access to his augmentation of or testimony about that thing" (13). The authority has, for reasons of superior wisdom, experience, or knowledge, privileged access to some body of knowledge; the subjects of authority, recognizing that privileged access, agree to defer to the authority's judgment with regard to the proper interpretation of that body of knowledge in particular cases. An authority in the classical sense is thus an intermediary between his subjects and a body of knowledge to which his access is direct, theirs wholly vicarious.

Now, some contemporary theorists of biomedical ethics resent the idea that physician professionalism is rooted in the physician's technical expertise. The physician, they protest, is more than a mere technician. But of course, the account I just gave of the exercise of the physician's professional authority is hardly an account of "mere" technical expertise. To bring a body of knowledge properly to bear on a unique, individual problem is an act of artistry.

There is a close relationship between the idea of grounding the professional morality of medical practice in the expert authority of physicians and that of grounding it in the vulnerability of the patient. To what, after all, is the patient vulnerable? Certainly to illness, but this raw fact cannot confer professional status upon the physician unless it confers such status also upon traditional healers and alternative therapists, and perhaps also upon parents, all of whom work with people who are vulnerable to illness. No, what the patient is relevantly vulnerable to is the physician's authority — that is, to its potential misuse. Of course, medicine has no monopoly on that kind of vulnerability. We are, after all, vulnerable to all kinds of authority. The misuse of other professionals' authority can land us in jail or worse. Mistaken applications of rational/legal authority can kill, or can impose great hardship. (Think about bureaucratic decisions regarding emigration or the issuance of a driver's license.) Our vulnerability to charismatic authority is notorious.

But physicians' professionalism is grounded in their expert authority because it is the nature of their authority that makes their professionalism necessary. They know something that neither their patients nor society at large can know. Both their patients and society are therefore vulnerable to professionals' misuse of their authority. Patients and society accept the professional's word as reason to believe or disbelieve, to act or to refrain from acting; if professionals are poorly trained or greedy or careless, they will believe or act wrongly, sometimes with devastating consequences. Only by their professionalism can they establish sufficient trust in the minds of their patients — and of society — to allow them to exercise their authority.

Physicians as Mediating Between Individuals and Society

Our discussion of vulnerability to misuse of authority leads to the question, on whose behalf does the professional exercise authority? One standard answer is that physicians must exercise their authority in the patient's best interest. But the Parsonian model reminds us that, as important and central to the morality of medicine as the individual encounter between doctor and patient has always been, that encounter has never been the affair of those two parties only. Healing, like illness, has always had a social side. Normally, the patient's goals and social goals are in alignment, but this is not always the case. Sometimes the physician needs to carve out some social space on the patients' behalf. And sometimes — though rarely — the physician needs to contradict the patient's wishes for the betterment of society by returning a patient to a state of mental health which he does not want; or by healing his burns even though the patient would, at the moment, rather die; or by declining to offer him any more hope.

The public trust held by professionals has not been sufficiently celebrated — or investigated. We often call attention to the special character of the physician-patient relationship, but seldom recall that every professional encounter has implications for the broader community. The actions and pronouncements of doctors often frame the social relations of their patients with their families, peers and employers. A word from a physician can trigger powerful social forces — can set in motion the social machineries of sympathy and accommodation, or stop them cold; can relieve a patient from obligation by naming his illness, or subject him to recrimination for complaining when there's "nothing wrong."

The physician's authority over the patient is thus also authority over the patient's community. He must therefore retain the trust of both, or else render his authority suspect and his expertise useless.

The Professional's Motivations

Professionals, Parsons argued, are as self-interested as any other successful actors in the contemporary capitalist economy, but their interests are in status and reputation rather than in political power and wealth (5). This affords a crucial counterbalance to the professionals' right of self-regulation: for while the right of self-regulation implies that professionals could not be induced by regulators into favoring the public interest over that of their private clients, the non-pecuniary character of professionals' dominant interests helps guarantee that they could not be induced to favor private, moneyed interests over the interests of the public. Thus, professionals' non-pecuniary interests are mobilized to minimize and neutralize their pecuniary interests.

There is a subtle point to be noticed here about the purpose of professional institutions (including professional customs). Professional institutions are not supposed to make physicians into saints. Parsons was adamant that professional self-regulation can work, and the interests of patients and society can be kept in balance, even if physicians are systematically and energetically self-interested. What is required is only that their self-interest be non-pecuniary in character. It is easier to turn aside short-term financial temptation if one is certain of one's high social status. The prospect of making another dollar will not distract the professional who is single-mindedly dedicated to achieving not only medical excellence, but also a reputation for medical excellence. Let the concentration on status be mistaken by laymen for overbearing pride, and the single-mindedness for narrowness. If physicians, through their professional organizations, can cultivate the proper interests — in status, in respect, in reputation for skill, in peer recognition — then their relentless competitive pursuit of these interests cannot hurt, and may even help, the rest of us.

It follows that patients and society are deeply threatened when physicians' professional institutions lose their way, and instead of attending to the issues they should be attending to — publicly articulating ethical and scientific standards, maintaining excellence in training, securing social status and recognition for physicians, fostering competition among physicians for medical publication and for public recognition, policing physicians by means of peer-review, and so on — they waste the "status-capital" of the profession by lobbying for pocketbook issues, training physicians to concentrate on money, and battling for political clout. And it is not only destructive for physicians' professional associations to concentrate on such things. It is destructive for physicians themselves to concentrate on them, even in the face of declining salaries (declining autonomy is another matter!). The authority of every physician is eroded whenever (and to the extent that) patients or the community perceive that professional opinions can be bought, either with dollars or with the promise of future political clout.

Unfortunately, a number of forces have in recent years conspired to motivate physicians to concentrate on pecuniary and political ends, rather than on professional ends. Perhaps the most dangerous force was the entry of the government into health care as a major payer. The greatest danger of Medicare and Medicaid to the medical profession was not, as the AMA originally feared, that medicine would be "socialized." It turned out rather to be that the practice of medicine became, for perhaps two decades, extremely profitable — more profitable than ever before. This was partly because Medicare and Medicaid were relatively generous in their first years, and partly because the creation of the programs legitimated and greatly spurred the growth of private health insurance. The new profitability of medicine undermined the professionalism of physicians by encouraging them for the first time to enter, in large numbers, into health care delivery *as investors*. And it further injured their professionalism by allowing them to get used to making large incomes while paying little attention to economics (18, 19).

This cast of mind made the marketplace developments of the 1980s — the federal government's decision to extend antitrust enforcement to the medical sphere, the general rise in the intensity of medical market competition, and the advent of aggressive cost-control measures by public and private insurers alike — even more threatening to medical professionalism than they otherwise would have been. It has meant that, for the last two decades, the profession's response to the dangerous assaults on its status, its autonomy and its authority has been mixed up with its response to assaults upon its income. This has of course hurt the defense of physician professionalism politically, because it allows politicians, health-policy academics and insurers to mouth the half-truth that physicians' complaints are "only about money." But the greater damage has been internal to the profession. When physicians and their schools and their professional associations are preoccupied with struggles involving money (or the political power with which to obtain it), professionalism — and the trust in authority that it props up — is seriously threatened.

Acts of Profession

Is it possible to shore up physician professionalism? Perhaps. There are, after all, important features of medical care that seem to dictate that it is most efficiently delivered by expert authorities (20). Surely the world would work better if patients and the community could feel comfortable trusting in those authorities, without worrying whether the judgment of these authorities is tainted or biased by pecuniary or political interests.

How is such trust to be re-established? Only through acts of profession. What are acts of profession? The "pro-fession" of professionals is fundamentally a speaking-forth in public, before the world and before one's fellow professionals. It is a public commitment to obeying socially accepted standards both of morality and of competence in one's work (21). Professionalism at its core has nothing to do with the secret handshake or the private network of connections — though, in nice Parsonian paradox, the pleasure of sharing a secret gesture or the communicative efficiency of a private network can surely help secure and facilitate professionals' commitment to their shared professional mission. Commitment to that mission is publicly announced whenever codes of ethics are published or cited or held up for admiration; whenever journal articles argue for improved medical technique or higher ethical standards; whenever obituaries or biographies or testimonial dinners celebrate the contribution of a physician to his or her field. It is also reaffirmed — as Ed Pellegrino has often reminded us — in the conversations between physicians and patients and their families (22). These are the acts of profession — the promises made by physicians to their patients and to their communities that they will use their expert authority wisely, and will not abuse it for the sake of money or power.

But how — after the 1960s' academic skepticism about professionalism and professionals' motives, after all the late-twentieth-century battles about HMOs and money and physician unions, after the attacks on medicine's scientific basis, after all the failures of competence and ethicality that any patient anywhere has seen or read about — can the medical profession expect that its promises will be believed? How can patients and the public be persuaded of the trustworthiness of medical professionals?

Of course, there is no easy answer. Professionalism, like love, has only the mode of being of "possibility." Its presence at any given moment is impossible to verify; its manifestations in conduct and language can always be explained away by reference to some ulterior motive. To prove our love to others, we can only love them. To prove their professionalism, physicians can only act as professionals, striving always to deserve the trust and admiration they hope to inspire.

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Professionalism and Clinical Autonomy in the Practice of Medicine

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Abstract

Professionalism in medicine requires a reasonable measure of freedom for physicians to determine patients' needs based on their own judgment. However, because virtually every medical decision is also a spending decision, third-party payers concerned about rising health care costs have introduced cost-containment tactics that significantly limit physicians' accustomed autonomy. In response, groups of physicians have filed class-action lawsuits against managed care plans, alleging causes of action such as fraud, breach of contract, extortion, and violations of federal RICO (Racketeer-Influenced and Corrupt Organizations) law. Such litigation may have merits, but it also faces significant obstacles, in part because the contracts involved may not actually have promised the broad measure of clinical autonomy that the physicians allege was promised, then denied. As physicians seek to restore and retain their professional autonomy, it will be important for them to be increasingly proactive in structuring or modifying the contracts under whose terms they practice — as some physicians have successfully done.

Key Words: Professionalism, law, RICO/racketeering, clinical autonomy, cost containment, managed care.

Introduction

As the other articles in this issue indicate, professions are defined by many characteristics — specific features such as an esoteric body of expert knowledge, and certain values and obligations such as a fiduciary duty to place the patient's interests above the professional's own interests. This article will focus on one fairly narrow aspect of medicine as a profession, namely, the need for clinical autonomy and independence of judgment.

This autonomy is not to be understood as some sort of petulant freedom to do or demand whatever one wants, or as a freedom to ignore the rules of law or the needs and interests of other people. Rather, it stems from a recognition that professions concern matters of enormous complexity for which simplistic formulae are inappropriate and impracticable. Science and standard routines will of course guide much of clinical care. Yet it cannot be certain whether a given patient will fit the norm until a knowledgeable, experienced physician actually examines that person. The patient may have an atypical presentation of a common illness or a typical presentation of a very uncommon condition; he might have anomalous anatomy defying standardized surgical techniques; he may exhibit unusual side-effects to medications that suit most people well; or he could have personal preferences that require revisions in the usual course of treatment.

This pivotal need for judgment that attunes general precepts to individual variations characterizes all professions, not just medicine. No "cookbook" can tell an attorney precisely how to litigate a particular criminal indictment or civil suit, because so much depends on the specific facts being alleged; existing precedents (or lack thereof) in that jurisdiction; the predilections of various personnel, including that case's jurors, judge, and opposing attorneys; and the preferences of the client.

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In medicine, however, a special challenge arises from the fact that health care is often very costly, and from the fact that third parties generally cover those costs. The latter is not ordinarily the case in other professional relationships. The attorney, architect, and engineer typically bill clients directly for their services, and clients can take costs into account however they wish as they decide what sort of services they want to purchase. But in medicine, the decisions that would otherwise be made by physicians in consultation with patients are now heavily constrained by payers' decisions about whether a proposed treatment is "medically necessary" and appropriately cost-effective. This intrusion of payers into the health care decision-making process has significantly curtailed physicians' accustomed professional independence.

This article briefly reviews the history of this challenge and then explores a special twist currently posed by class-action litigation that has been brought against several health plans. Finally, the article will make some suggestions on how physicians might exercise personal involvement and responsibility, to preserve a measure of professional independence even in the face of broad and conflicting financial demands.

History

Prior to the proliferation of health insurance during and after World War II, patients paid for medical care out of pocket — it was not usually an overwhelming burden, since medicine had relatively little to offer. Technologies and improvements in hospital care began to emerge during the post-war years, but with insurance steadily becoming a standard workplace benefit, physicians and patients still felt few financial constraints on their decision making. This pattern was solidly entrenched with the passage of Medicare and Medicaid legislation in 1965. These government programs, and soon thereafter private insurers, generally paid providers according to their "usual, customary, and reasonable" fees, rarely challenging what physicians chose to order for the care of their patients. Physicians, after all, had the professional expertise, and it ill behooved insurers to challenge their medical judgments (1–4). Such policies created an "artesian well of money" (5) in which physicians, for the most part, could care for their patients however they wished, and patients could accept whatever was offered, secure in the knowledge that all would be paid for. Even uninsured patients could receive virtually the same level of care as everyone else, once they were accepted into the system, through a cost-shifting in which providers charged more to those who could pay in order to cover those who could not.

By the early 1970s it was obvious that such a system was highly inflationary, as costs were beginning to escalate out of control (6, 7). Numerous attempts at cost containment — ranging from President Nixon's wage- and price-controls, to President Carter's quasi-voluntary hospital price limits, to Medicare's Diagnostic-Related-Group payment system, to corporations' mandates for second opinions to justify high-cost care — failed to stem soaring costs (2). Finally, in the late 1980s and early 1990s, business firms, watching their international competitive position erode because of their inability to control the huge cost of employee benefits, finally demanded change. "Managed care" became a major force, and in 1993, for the first time in several decades, annual increases in per capita health care expenditures were less than two percent (8).

This "taming" of health care costs came about through wide-ranging and often vexing changes in the ways health care has been financed and delivered. Tools have ranged from intensive and sometimes intrusive utilization management and gatekeeping arrangements, to denials of payment, to financial incentives such as withholding pools, bonuses, penalties, and capitation arrangements. Physicians "game" their way around the rules (9–12), while health plans game their way around the physicians and reinvent the rules (13–18). If the consequences were not so distressing, the scene would be a comedy of herding cats.

Still, cost-containment tactics in one form or another are surely inevitable. Virtually every medical decision is also a spending decision. So long as third parties incur the financial consequences of physicians' medical/spending decisions, they must and will attempt to limit their economic liability. They can do so either by controlling the spending directly, in which case they effectively control or at least circumscribe the medical decisions (as in utilization management) or by transferring the financial consequences of the decisions (as in risk-shifting arrangements) (19). Either way, the clinical autonomy to which physicians had become so comfortably accustomed as their right of professional independence is now significantly limited.

Managed Care Litigation

Physicians have not accepted these changes passively or altogether peaceably. Some of the more forceful responses are found in lawsuits filed by providers, paralleling similar suits filed by patients, challenging health plans' strategies for containing the costs of health care. A plethora of provider-filed suits has now been consolidated into a single class-action suit (the "provider-track") (20); similarly, a number of patient suits have been consolidated into a parallel class-action suit (the "subscriber-track") (21). Although this article does not offer an extensive discussion of these suits, it will be useful to summarize two key elements in the providers' consolidated complaint.

Alongside fraud, breach of contract, extortion, mail and wire fraud, and assorted other causes of action, the suit alleges violations of the Racketeer-Influenced and Corrupt Organizations Act (RICO, the federal anti-racketeering law, 18 U.S.C., 1961 – 1968). That is, the complaint alleges that health plans across the United States have engaged in a pattern of racketeering activity, "defined as behavior that violates certain other laws" (22, p. 1079) such as extortion, fraud, mail fraud, and wire fraud. Among other concerns, the suit argues that the health plans made, and broke, two major promises.

First, the plans allegedly promised that physicians would be able to exercise independent judgment, free from improper interference and control. Second, they promised to provide physicians with adequate compensation for their services. In reality, the complaint says, health plans have failed to disclose important policies and practices that resulted in delays, denials, and decreases of payment; they paid unconscionably low rates, whether in a fee-for-service or in a capitated setting; and in risk-sharing situations such as those involving pharmaceutical benefits, they transferred unacceptable levels of risk to physicians. Moreover, the defendant health plans systematically interfered with physicians' medical judgment, thereby impeding physicians' ability to fulfill their professional obligation to provide appropriate care and interfering with the trusting relationship between physicians and their patients.

In essence, the complaint portrays a "catch-22" situation. On the one hand, physicians who provide care within the constraints of the health plans' payment policies risk loss of trust, reputation, and profession, and in the process increase their exposure to legal liability. Conversely, if the physicians' care comports with the accepted medical standard of care, the plans punish them with nonpayment, inadequate payment, delayed payment or other coercive tactics. All this, the complaint notes, is done to increase the defendant health plans' profits.

Accordingly, the suit asks for declaratory and injunctive relief to require plans to cease such tactics; for attorney fees and the costs incurred in bringing the suit; and for whatever other relief the court deems appropriate. The latter could include financial damages that, under RICO, would be trebled.

Although it is difficult to predict whether the litigation will succeed or fail, two recent court decisions address related issues and, in the process, speak to broader questions about physicians' autonomy and professionalism.

Related Cases

The Supreme Court's decision in *Pegram v Herdrich* (23) addresses the question of whether it is legitimate for for-profit health plans to engage in cost-containment practices such as incentive schemes. In the context of complex issues concerning the federal Employee Retirement Income Security Act (ERISA) law of 1974, that governs workplace benefits, the Court opined that such financial constraints were not inherently illegitimate, even though they may increase the risks of some kinds of undesired outcome. "Since inducement to ration care goes to the very point of any HMO scheme, and rationing necessarily raises some risks while reducing others (ruptured appendixes are more likely; unnecessary appendectomies are less so), any legal principle purporting to draw a line between good and bad HMOs would embody, in effect, a judgment about socially acceptable medical risk" (23, p. 2150). If cost-containment measures such as incentive schemes are to be restricted, it is the legislature, not the courts, that must do so. Moreover, neither is it the Court's place to outlaw health plans that operate on a for-profit basis. After all, since "the provision for profit is what makes the HMO a proprietary organization, [Herdrich's] remedy in effect would be nothing less than elimination of the for-profit HMO. . . . [T]he Judiciary has no warrant to precipitate the upheaval that would follow. . . ." (23, p. 2156).

Accordingly, if the current anti-managed-care litigation proposes that courts should force health plans to refrain from providing incentives to physicians to constrain care or from making profits, the Supreme Court would seem to disapprove. If incentive systems pose undue hazards to physicians' clinical autonomy and thereby to the content of patients' care, then it is for the legislature, not the courts, to rule them out. Thus far, no legislature has chosen to do so.

A second recent decision comes from the federal Third Circuit Court of Appeals in *Maio v Aetna* (24). Analogous to the providers' class-action suit described above, *Maio* featured a class-action RICO suit brought by patients against Aetna US HealthCare. Patient-plaintiffs alleged a substantial gap between what the plan promised and what it delivered, largely because the plan's cost-containment policies allegedly discouraged physicians from providing appropriate health care. That gap, they argued, added up to fraud and other assorted offenses, thereby representing a pattern of racketeering violations.

The Third Circuit rejected plaintiffs' claims on several grounds, one of which is particularly pertinent here. The court took note of the actual contractual language by which the health plan made its promises to enrollees. That contract does not promise what plaintiffs claim, the court observed. Aetna never promised to permit (or pay for) physicians to order whatever services they wished. In contrast to plaintiffs' claims, "Aetna promised to provide its members with a different contractual benefit — namely the right to receive covered health care benefits in the form of medically necessary supplies, health care services and treatment through Aetna's participating providers" (24, p. 491). Moreover, the contract explicitly reserved the right for the plan, not the physicians or enrollees, to determine which services are medically necessary. Thus, the so-called gap between what was promised and what was provided fades considerably once one looks more closely at the actual contractual promises. As a consequence, the allegations of fraud and racketeering likewise failed to stand up.

This emphasis on contract is highly relevant to broader issues about physician professionalism and autonomy in the face of medicine's economic overhaul. The complaint in the provider-track of the current class-action suit seems to imply that the defendant health plans promised physicians essentially the same sort of independence and clinical autonomy that physicians exercised during the days of the "artesian well" — the freedom to provide virtually whatever care they wanted and to charge virtually whatever they saw fit, with almost unquestioned assurance of being paid in full. As noted above, those days are gone. While the actual contracts featured in this particular litigation are not available for review by the readers or the author of this article, it is reasonable to be at least somewhat skeptical that those contracts actually promised "artesian" freedom. Perhaps the independence they promised was instead the sort that health plans commonly promise today: physicians are free to provide care however they wish, but health plans are also free to refuse to pay for it, in accordance with the coverage terms of the contract. As in the *Maio* case, the plans may have retained the right to make their own decisions about which care is medically necessary and thereby covered.

If indeed the various contracts made limited rather than "artesian" promises, then the racketeering allegations may fail, for the same reasons as in the *Maio* decision. There is no fraud or extortion, nor any pattern of it, if the promises match what is delivered — even if some observers might argue that those promises are considerably more modest than they should be. Accordingly, at this point it seems appropriate to discuss some deeper issues concerning, first, the importance of clinical autonomy in the practice of medicine, and second, the role that physicians should take in ensuring that they practice with an adequate measure of autonomy.

Deeper Issues

The Scope and Focus of Clinical Autonomy

The first issue — inquiring just how much clinical independence physicians really ought to have in order to provide good care — is as complex as it is important, and will not be the focus of extensive discussion here. Readers are referred elsewhere for a detailed consideration of the question (25), but a brief summary would nevertheless be useful.

Although a measure of independent judgment is very important in any profession, for the reasons outlined above, the extraordinary independence physicians exercised during the days of the "artesian well" was not always in patients' best interests. Partly because physicians were so free to do whatever they saw fit, and partly because scientific research focused mainly on the development and approval of costly new technologies rather than on the more mundane modes of clinical care, physicians' clinical practices came to vary quite widely. As noted by Wennberg (26–29), among a host of other observers, medical practice variations came to reflect, not always the medical differences among patients, but such ancillary factors as availability of beds and facilities, and local fashions and customs (30–32). In addition, physicians too often failed to implement even ordinary forms of care that were known to be effective and cost-effective, such as prescribing aspirins and beta-blockers for patients surviving myocardial infarction, or ACE inhibitors for patients with congestive heart failure (33–37).

The introduction of evidence-based guidelines can serve as an important antidote to unfounded variations in care. Such guidelines can help physicians to remember a host of factors that are otherwise difficult to keep in mind, such as who needs which preventive care and when. They can also incorporate the latest information for a faster dissemination of improvements in clinical care, and they can help to reduce rates of error (38–42).

Still, it is obvious that guidelines cannot replace the clinical observation, judgment and experience of a physician. Physicians need to retain substantial clinical autonomy for at least two major purposes. First, they need freedom to render appropriate care when a particular patient does not fit the applicable guidelines. No guideline can adequately anticipate the patient who does not respond as expected to a given medication, whose presentation of illness is atypical, or whose preferences create adherence challenges. In these cases physicians cannot deliver adequate care without adequate freedom to deviate from guidelines. This does not mean that health plans must finance unlimited freedom for physicians to deviate whenever they please, because that would represent a return to the "artesian" financing that has become fiscally unsustainable. However, it does require appropriate procedures whereby physicians can make and implement their own judgments without undue impediment. This is particularly the case for the ordinary ailments seen in the great majority of clinical encounters. A relatively small number of patients consume the vast majority of resources (43), and it is in this area that health plans should ideally focus their greatest attention, not by endlessly diddling in the daily details (44).

Second, physicians need an avenue by which they can help to reshape guidelines that are clinically or scientifically ill-founded or outdated. In some cases the guidelines by which health plans make decisions about care and coverage are the product, not of science, but of actuarial data or of a short-sighted focus on costs without adequate attention to evidence or to consequences (25). Where that is the case, physicians should have a strong voice in modifying the guidelines by which their care is guided, evaluated, and paid for.

Physicians' Obligations in Protecting Clinical Autonomy

One of the most complex, yet relatively undiscussed, aspects of the class action lawsuit concerns the question of how these physicians came to be contractually bound by such allegedly onerous conditions. The payment rates are unconscionably low, the complaint says, and physicians are effectively forced to provide inadequate care.

On the one hand, physicians in at least some areas of the country face a difficult predicament. Where a small number of very large, powerful managed care organizations provide health care coverage for a great majority of the people in a particular geographic area, the average physician may have limited alternatives to contracting with those plans, if he or she wishes to remain in that locale. For instance, "five HMOs control nearly 90 percent of California's HMO market. A total of 300 physician groups operate in the same market, giving enormous bargaining power to the HMOs" (45, p. 1067). The challenge is compounded by the fact that, if otherwise-independent physicians conspire together to insist on a better fee schedule or to boycott the health plans with whose terms they are dissatisfied, they can be guilty of antitrust violations — including so-called *per se* violations that carry treble damages (46).

And there is yet another side. Ostensibly, these physicians signed their respective contracts voluntarily. No one held a gun to anyone's head. If physicians agreed to ethically dubious terms, they must accept a measure of responsibility.

In the end, the answers will surely be as complex as the problems. On the one hand, health plans have an obligation to negotiate honestly and to fulfill their agreements in good faith. Courts have agreed. In one case, for instance, a dental HMO consistently failed to provide its provider-dentists with accurate lists of enrollees. The plan was capitated, and providers needed that information in order to know whom they were obligated to serve, and to manage their budgets appropriately. Because the dentists had no alternate means of verifying which of their patients were enrolled, the dentist group "could not determine who to treat or how much capitation it was owed. More important, without accurate eligibility data, the dental HMO would not even realize if it were being underpaid" (47, p. 194). The group was entirely dependent on information provided by the plan, and the plan knew that to be the case, yet did not provide the correct information. Accordingly, a Texas appellate court found that the health plan had violated a special duty of good faith and fair dealing (47).

Indeed, physicians' lack of negotiating power is perceived to be so significant in certain regions that some physicians have joined together in union-like associations to bargain collectively (48–50), although a recent Supreme Court decision casts significant doubt on whether physicians can successfully unionize (51). Other physicians have used litigation, or the threat of it, to work out special arrangements with health plans, as physicians and others did regarding Aetna in Texas (52, 53). More broadly, some commentators support legislation to provide physicians with some relief from antitrust constraints, in hopes of permitting more evenly matched negotiating (54, 55). The question of whether and to what extent physicians need to increase their bargaining leverage depends at least partly on empirical analyses of each side's market power and negotiating strength — analyses that have not yet been undertaken in any systematic way.

On the other hand, physicians themselves must shoulder some major responsibilities if they are to preserve a measure of the clinical independence needed for serving their patients well. Perhaps at the top of the list, they must now learn to scrutinize prospective contracts — or more realistically, to hire knowledgeable people to do it on their behalf — and refuse to sign on to arrangements that they find ethically, financially, or medically intolerable.

This is not a task to which many physicians are accustomed. As noted by one commentator (56, p. 191):

> Too often, doctors sign managed care agreements without reading them; other times, doctors don't keep copies, so they can't verify whether the terms are being met. Sometimes, doctors don't even tell their office manager which contracts they've signed. Physicians also fail to seek advice from readily available sources, such as their state medical associations.

Though they may find the task distasteful, physicians have little alternative. In many cases, physicians can exercise considerably more bargaining power than they realize. In one case, for example, the health plan covering employees for a very large corporation insisted that its fee schedule and contract terms were not negotiable. The physician group providing care for these employees found those terms to be unacceptable and directly informed the employer. After a nine-month standoff, the plan offered a significantly improved contract (56). With the help of advocates skilled in such negotiations, physicians have been able to: improve the fees a health plan pays, particularly for higher-volume interventions; remove the "hold harmless" clauses that can potentially leave physicians exclusively liable for treatment decisions, including denials of care, that lead to adverse outcomes; limit the array of services physicians are required to provide under a capitation arrangement; obtain a health plan commitment to pay claims within specified time-limits, such as thirty days; and secure disclosure of (and thereby place appropriate limits on) the formulae for bonuses and withholds (56–63).

Conclusion

Physicians across the nation are understandably bewildered by the dramatic changes that have substantially constricted their ability to make decisions with the independence to which they had been accustomed. Some of that loss is regrettable, yet the situation is not hopeless, even if it requires physicians to take greater responsibility for the conditions of their own practice.

One major task for the profession as a whole is to create more coherent, evidence-based patterns of care. If physicians are to expect patients and payers to "trust me, I'm a doctor," they must make good on the profession's promise to provide a scientifically well-founded approach to care that can documentably produce the best outcomes for patients.

In the same spirit, physicians must also take a more active role in the conditions of their work. If physicians are to regain and retain an acceptable level of professional autonomy, they cannot expect others to do that task for them. Other players in this fast-changing scene have their own responsibilities, including patients as well as payers and employers. As fiduciaries of their patients, physicians have a professional obligation to make sure that the conditions under which they agree to practice do not place them under untenable restrictions or conflicts of interest. Accordingly, physicians must take a much more active role in studying, understanding, and appropriately modifying the contractual terms under which they practice. It is not acceptable to point to others and say "they made me do it," if the physician has not read the contracts that, per his agreement, will define or restrict his practice as well as his income.

In the end, the current situation, while challenging, presents an important opportunity to bring a new rationality and coherence to the structure of health care. And it provides an opportunity for physicians and health plans alike to consider more carefully the ways in which physicians need clinical independence and professional autonomy as prerequisites to providing good care, and the ways in which that autonomy can best be secured.

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Professionalism, Profession and the Virtues of the Good Physician

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Abstract

The putative loss of "professionalism" in medicine has of late become of serious concern to practitioners, educators, ethicists and the public. Impassioned pleas for its restitution abound. Serious ethical obligations are linked to the idea of a profession. Yet, most of the definitions have been socio-historical, political or legal. Important as these aspects may be, there is need for a firmly grounded ethical derivation of the moral dimensions of professionalism. This essay undertakes to provide a philosophical grounding for ethically responsible professionalism in the phenomena of clinical medicine, in the character of the professional, and in virtue theory.

Key Words: Professionalism, profession, virtue, virtue ethics, medical education.

PROFESSIONALISM, the process of professionalization, and teaching of professional behavior have become dominant concerns of medical educators, practicing physicians, and professional associations. Others have already sketched in the historical and sociological determinants of professionalization, and its codification in the Oath of the Hippocratic School. Against this background I will examine the place of the virtues of professionalism in medicine and to delineate the ethical foundations of medical professionalism.

I will divide my discussion into four brief parts: (a) a brief note on definitions and connotations of the terms profession and professionalism; (b) a short outline of the concept of virtue ethics; (c) the place of virtue ethics in the medical profession; and (d) teaching the medical virtues.

Professionalism and "Profession"

"Professionalism" has come to be accepted as a watchword for those qualities and modes of conduct proper to professions. In common usage, professions have often been defined in the following terms: possession of a body of special knowledge, practice within some ethical framework, fulfillment of some broad societal need, and a social mandate which permits a significant discretionary latitude in setting standards for education and performance of its members (1). On this view many occupations in modern society lay claim to the sobriquet of "profession."

Traditionally, a much smaller number of professions, by virtue of their educational breadth and their importance in satisfying some fundamental human need, have been called "learned professions." Medicine, law, ministry, and sometimes the military and the academic occupations have enjoyed this special status. They meet the criteria for a sociologically defined profession but they also occupy a special niche among the vast number of occupations that now lay claim to professionhood.

That special claim lies less in their expertise than in their dedication to something other than self-interest while providing their services. That something else is a certain degree of altruism, or suppression of self-interest when the welfare of those they serve requires it. This is the distinguishing feature of medicine, ministry, law, and teaching that sets them apart. They are in this sense "professed," i.e., publicly commit-

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ted to the welfare of those who seek their help. They thereby become ethical enterprises and it is this dimension of the profession of medicine that I shall focus upon in this essay.

"Profession" means, in its etymological roots, to declare aloud, to proclaim something publicly. On this view professionals make a "profession" of a specific kind of activity and conduct to which they commit themselves and to which they can be expected to conform. The essence of a profession then is this act of "profession" — of promise, commitment and dedication to an ideal.

In medicine this act of profession occurs in two ways. One is the public profession — the solemn proclamation on graduation from medical school when the "Oath" is taken. This is the moment when the newly graduated physician enters the profession, not when she receives her degree. The degree is simply evidence of completion of the academic requirements for the degree "doctor of medicine." It says nothing of the commitment to the way the acquired knowledge and skill are to be used. Without the Oath the doctor is a skilled technician or laborer whose knowledge fits him for an occupation but not a profession.

When the Oath is proclaimed, if it is taken seriously as a binding commitment to place one's special knowledge and skill at the service of the sick, the graduate has then made his "profession." He or she enters the company of others with similar commitments. At this moment, one enters a moral community whose defining purpose is to respond to and to advance the welfare of patients — those who are ill, who are in need of help, healing, or relief of suffering, pain or disability.

The second way the profession is "declared" is in the daily encounter with patients. Every time a physician sees a patient and asks "What can I do for you, what is wrong, what is the problem?" he or she is professing (committing oneself) to two things: one is competence (i.e., having the knowledge and skill to help) and the other is to use that competence in the best interests of the patient. This "profession" or commitment, by its very declaration, invites trust. The doctor voluntarily promises that he can be trusted and incurs the moral obligations of that promise.

Implicitly, this same silent commitment obtains in every visit between physician and patient. If it were not understood as such, the patient would never consult the physician. This implicit profession persists even if the relationship is not ideal and even if there is some mistrust or hostility. Whatever uncertainties there may be in the relationship, to be effective in helping the patient it must have a residuum of trust and the physician must be faithful to that trust.

Professionalism on the other hand is a somewhat different concept. Unquestionably it has been equated by many educators and professional groups with some of the characteristics of a profession that I have outlined. These groups are concerned about "deprofessionalization," i.e., the defection from the moral demands of a profession. However, professionalism itself can also connote certain features which are less commendable ethically.

I refer here to such characteristics of "professionalism" as unquestioned loyalty to other members of the same profession, a certain exclusivity and elitism based on credentials, and a concern for titles or self-interests common to the group. In its more distorted forms professionalism can become an ideology, or a symbol of a guild; it can generate a union mentality focused on defending the group's own interests. It is all too often expressed in the self-protective, retaliative and bureaucratic behavior of professional organizations.

These aberrant connotations are of course not what many well-intentioned educators mean but it is important to make it clear that the word "profession" essentially has a moral center that is not fully captured by professionalism and may even be antithetical to it. In any case, when discussing the virtues, I shall concentrate on the pristine notion of profession, in the sense that it first appeared in relation to the practice of medicine.

The first written use of the word "profession" in relation to medicine was in 47 A.D. in a book of prescriptions written by Scribonius, physician or pharmacist in the court of the Roman Emperor Claudius. In a few short pages having to do with the reluctance of his contemporaries to use medications, Scribonius referred to the "profession" of medicine. This he defined as a commitment to compassion or clemency in the relief of suffering. He did this in the context of one of the first references to the Hippocratic Oath in ancient literature, arguing that the proper use of drugs was consistent with the Hippocratic injunction to help and heal the patient (2–5).

Scribonius also outlines other moral precepts that he relates to the Hippocratic "profession" — the bans on abortion and euthanasia, and the requirement to always act to help the sick by whatever means are available. Scribonius presents a humanistic interpretation of the profession and links that humanism to certain virtues like benevolence, compassion, mercy and competence in the use of medication.

Extending this discussion into the full history of the word "profession" is beyond the scope of this article. Suffice it to say that the word "profession" has been linked with the virtues from its first usage. Indeed, the ethics of the profession was, until very recently, a virtue-based ethic which associated the good physician with certain character traits. The personal ethics of some of the most worthy physicians in the history of medicine was a virtue ethic — e.g., physicians of the Confucian, Hindu, or Hippocratic schools. In modern times the ethics of Thomas Percival, Francis Peabody, William Osler and Florence Nightingale were essentially virtue based.

Before linking specific virtues to the profession of medicine it is useful to review concisely the notion of virtue as a basis for ethics.

Virtue Ethics in General

Virtue-based ethics is the oldest and most durable system of ethics in both Western and Eastern cultures. It is a system that concentrates on the moral agent and the kind of person he or she ought to be, rather than on the acts themselves, the circumstances, or the consequences they produce. Until the Enlightenment, it was the dominant theory of ethics. In modern times it has persisted but has been superceded by other theories like deontology, utilitarianism, emotivism, etc. But all of these theories gave some account of virtue. In more recent times virtue ethics suffered erosion by the positivist and analytic approaches to moral philosophy. In the last several decades virtue-based ethics has enjoyed a renaissance, however, its ultimate place in moral philosophy is yet to be established firmly.

Currently there are three approaches to virtue theories of ethics: One is the so-called "thick" version, which reduces all of ethics to virtues. A second is the so-called "thin" version, which makes virtue one among many theories, but with no special claim. The third approach, which I shall follow here, is the complimentary version. On this view, virtue ethics is an essential element in any complete theory of the moral life. It cannot stand on its own, but it is also a necessary compliment to any other theory.

The reason for the indispensability of virtue ethics is the ineradicability of the moral agent in the moral life. All principles, duties and rules of ethics must ultimately be expressed in the moral life of the living human agent. How duties, rules, obligations, sentiments, etc., are acted upon, interpreted, given weight, put into priority and with what intention or motives, are all shaped by the character of the moral agent. The agent, therefore, cannot be left out of the judgment of the moral status of any particular human act.

As with so many other concepts fundamental to Western culture, Plato and Aristotle most aptly expressed the idea of a virtue. Plato associated it with the idea of excellence (*arete'*) in knowledge of good. Aristotle, like Plato, equated the virtues with excellence (6): "The excellence of man also will be the state which makes a man good and makes him do his own work well."

Elsewhere, Thomasma and I traced the concept of virtue from its origins to its revival in general ethics (7). Its revival in medicine has several origins. One is the growing reaction to the dominance of principle-based ethics which some consider too abstract or limited in its interpretation of the professional life. Another is the ineradicability of the moral agent and the place of the virtues in educating physicians. On the other hand, critics of the revival of virtue point to the absence of specific moral content and action guides or rules. They criticize the circular reasoning which defines "good" as what the virtuous person does and the virtuous person as the one who does "good."

Virtues are compatible with principles, as Beauchamp and Childress have emphasized in later editions of their influential work (8). Virtue ethics, however, can also be related to other theories of ethics via links to duties, obligations, rules, etc. The conceptual connections are not always easy to make and this is a task for virtue theorists in the years ahead. In the remainder of this article I will concentrate on the virtues specific to the profession of medicine in the pristine sense of the word "profession."

Virtue in the Ethics of the Medical Profession

Aristotle's definition of virtue seems most apposite for the profession of medicine since it links moral excellence (the moral virtues) with the kind of person the physician should be and with the excellence of the work he does specific to his profession. Let us examine the act of profession in relationship to the ends of medicine to see what character traits the physician must possess to achieve the ends of medicine with excellence (9).

Publicly in his oath and privately in his encounter with the patient, the physician professes two things — to be competent to help and to help with the patient's best interests in mind. This commitment invites trust which ultimately the patient must place, to some degree at least, in his physician. The purpose of the physician-patient relationship is healing, i.e., curing when possible, caring always, relieving suffering, and cultivating health. This is what is promised implicitly by the profession that the doctor makes whenever he enters the clinical encounter.

It is these ends which give content to virtue ethics in medicine (9). The good physician will be one who exhibits those character traits which most effectively achieve and indeed are indispensable for attainment of the ends of medicine. Some of the virtues entailed by the profession or commitment of the physician and the ends which actualize that commitment are:

- *Fidelity to trust* — because the physician has invited trust, the patient cannot avoid it, and it is essential if healing and helping are to occur.

- *Benevolence* — because the prime precept of medical ethics since the Hippocratic era has always been acting for the good of the patient, and of course, avoiding all harm.

- *Intellectual honesty* — because medicine is a powerful instrument for good and harm depending on how medical knowledge and skill are used. Knowing when one does not know and having the humility to admit it and to obtain assistance are virtues crucial to avoiding harm.

- *Courage* — because the physician must expose herself to the dangers of contagion, to possibilities of physical harm in emergency situations, and to political retribution in regimes that enlist physicians in torture, interrogation of prisoners, and deceptions of various kinds. It also takes courage to be the patient's advocate in a commercialized, industrialized system of care.

- *Compassion* — because in any chronic or complicated illness or clinical decision, the physician must enter the predicament of the patient, to feel something of the patient's plight if his scientific judgments are to be morally defensible and suited to the life of a particular patient.

- *Truthfulness* — because the patient is owed the knowledge necessary for making informed choices, so he can make plans for his own life when disease disrupts those plans, and so he can assess his doctor's competence to undertake what he proposes.

These are a few of the specific virtues entailed by the profession, the silent commitment made in every physician-patient clinical encounter. There are other virtues, of course, but these few seem essential if the end of medicine — the healing of this patient — is to be attained with some degree of excellence.

These are virtues generated by the nature of the medical encounter with individual patients. They are also essential for the practice of preventive medicine. They are crucial as well to the fulfillment of the responsibilities of physicians to society, in public health and organized medicine. Time and space allow only for mention of these extensions of the way virtues undergird the profession, individual physicians, and the organized profession as they meet the obligations incurred by their public declaration of expertise in the service of the sick.

Practical Implications

Critics of virtue-based ethics often accuse it of being without content, action guides, rules or duties. This is in part true, but it ignores the significant effect of a commitment to virtue on the conduct of the physician. It is difficult, for example, to imagine that a physician committed to the virtues I have just outlined would ever consider her relationship with the patient as primarily a commodity transaction, a contract for service, or the mere application of scientific knowledge to a sick organism. A virtue-inspired physician would recognize *pro bono* work as crucial to her stewardship of medical knowledge. Neither could such a physician see herself as an entrepreneur, an investor or as owner of a health care facility like a hospital operated for profit. She would not claim proprietary rights over her knowledge.

For the virtue-based physician, the relationship with the patient could not be a contract or a commodity transaction. It is a covenant of trust, a special kind of promise to serve those who require her expertise. Suppression of self-interest to some degree would be a natural corollary of a virtue-oriented physician. None of this is to deny that the virtue-based physician is also compelled on the basis of virtues of parent and husband to be faithful to his commitments to his family, friends and society. He would, however, recognize what the limits of legitimate self-interest are and when that set of interests should be set aside in the interests of his patient or vice versa.

This is where the central virtue of practical wisdom comes in. Aristotle described *phronesis*, the virtue of practical wisdom, as the capacity for deliberation, judgment and discernment in difficult moral situations. It is practical wisdom that unites the moral and intellectual virtues and helps the moral agent to resolve conflicts among virtues, to put them in the proper order of priority, and to make the right and good decision in the most difficult situations.

Practical wisdom is also the most valuable virtue for the physician as a physician. It is the habitual disposition to make right choices in complex clinical circumstances. The practically wise physician is not one who acts cautiously and self-interestedly to protect himself. That is the contemporary debasement of the word. Practical wisdom assists the physician in his choices and is the virtue of wise clinical judgment.

The virtue-based physician could never see his patient as a "customer," consumer, insured life or any other commercialized, industrialized transformations of the ancient and respectable word "patient." Nor could he compromise his personal or professional integrity for political, economic, or social advancement. Nor could the virtuous physician become a union member, go on strike, or engage in blatant self-promotion and advertising even though it is sanctioned by law. This would suit the ethics of professionalization but not of a true profession.

The virtuous physician would recognize that he is a member of a moral community united to those other physicians who have made the same act of profession or commitment to the welfare of the sick. She would see professional organizations and associations as extensions of the ethical and moral commitments that are shared with fellow physicians. The contemporary model of so many professional associations as corporate, money-making, lobbying, advertising enterprises is inconsistent with what the profession of medicine is about.

The virtue-based physician would see the importance of working within professional associations to change their character, to urge upon them the primacy of the patients' welfare and their advocacy for justice in health care. He would understand that withdrawal from professional associations is to abdicate the responsibility to transform them for the better. Indeed, if professional associations are to be rescued they will need physicians who are committed to an ethic of virtue.

Conversely, the virtuous physician cannot fully actualize his personal virtues unless there is a community of virtues to sustain and reinforce his commitments to the virtues. Alisdair McIntyre makes much of this point in his seminal study of the virtues in contemporary life (10).

It is in the conjunction of the moral community and the moral individual that Aristotle's conjunction of "The Politics" and "The Ethics" become a model for professionals and professional associations today. The aim of Aristotle's "Nichomachean Ethics" was (as it was for the entire classical medieval ethical synthesis) the formation of virtuous (i.e., good) persons. In his writing on ethics Aristotle defined the virtues of a good member of a society, and in his "Politics" he defined the good society and the virtues that such a society should exhibit.

On this view, ethics and politics (in the etymological sense of politics and not its modern connotations) are reciprocal elements of a moral whole. Good citizens make for a good society; a good society makes for good citizens. As medicine confronts the current crisis of professionalization and deprofessionalization the mutual moral interdependence of the individual physician and the professional society must be confronted. One cannot be reformed without the other, if anything resembling the pristine notion of profession is to be recovered.

Medical educators, medical practitioners and the leaders of professional organizations all share in accountability for our present state of deprofessionalization and for our success or failure in recovering some remnant of moral credibility. This, I believe, translates into character formation and virtue promotion in medical schools and in the conduct of the affairs of professional organizations. Neither entity is engaged in this recovery. Indeed, most indications are that medical education and medical professional associations have compromised or lost their moral credibility (11).

Can Virtue Be Taught? How?

This brings me to the last of my topics — if character is to be formed, virtues must be taught. But there are serious doubts about whether virtue can be taught or even if they could be taught, whether they could survive in our present society where self-interest, not altruism, is the rule of success (12).

The teachability of virtue has been a question since Plato's time. In his dialogue with Meno, Socrates was asked bluntly — at the very outset — "Can you tell me, Socrates, whether virtue is acquired by teaching or practice. . ?" (13).

Socrates as usual illuminated the question but did not answer definitively. Aristotle, on the other hand, did so definitively. He said we learn by practice and that the best practice is to follow a model of the virtuous person. In medicine this means we need virtuous physicians as teachers. Basic scientists often provide such models for medical students, but more often it is respected clinical teachers who provide the example in their conduct of the physician-patient relationship.

Once a medical student or resident has chosen a field for concentration or specialization, consciously or not she shapes her self-image as a physician. She begins, in fact, to practice the virtues (or vices) of that model. The more morally mature the student is, the more she will distinguish the virtues from the vices. But the less mature will conflate the two, since they lack the practical wisdom to discern the difference. Clinical teachers thus bear a heavy responsibility for the character traits that they model for their students and residents.

If there is one essential element in the effort of a medical school to shape the professionalization of its students, it is the dominant concept of profession that defines its faculty, especially its clinical faculty. Character formation cannot be evaded by medical educators. Students enter medical school with their characters partly formed. Yet, they are still malleable as they assume roles and models on the way to their formation as physicians.

While role models are the most powerful force in professional character formation, certain ancillary educational efforts can also shape the developing physician more than modeling. Courses in medical ethics, the humanities, human values, etc., can sensitize, raise awareness and force critical reflection about the virtues of the good physician. Courses introduce students to a body of literature which gives evidence of the importance, depth and complexity of the moral issues commonplace in medical practice. They challenge the reflective student to at least examine, verify, assimilate or reject what he is being taught or what he sees in faculty behavior.

Medical history and literature also add to this process of character formation by offering students an acquaintance with historical figures as models. One has only to ask today's students if they have ever heard of William Osler, Francis Peabody or William Harvey to appreciate how neglected this form of character formation has become. The figures they are more likely to be exposed to are corporate entrepreneurs, power players in the health care industry, athletes and entertainment celebrities.

In any case, if the profession is to be resuscitated as a moral enterprise and not a branch of high-tech industry, medical schools will need to give significant attention to inculcating the virtues and to evaluating their students and faculty, and their institutional behavior by these standards as well.

Professional societies, if they are to be true to their claim to represent the profession, should recapture the notion of profession and de-emphasize the guild-like connotations of professionalism. Here too there is a need for physicians with the virtue of courage sufficient to enable them to stand clearly and visibly for what makes medicine a profession. This will mean leadership of a kind that eschews self-interest and truly advances the welfare of patients as medicine's raison d'être.

Unfortunately, today many professional associations are preoccupied with financial survival, corporate growth, investment strategies, benefits for members, fees for testimonials, etc. There is little energy left for promulgation of the ethical purposes of the profession as a profession. In these respects professional medical associations seem to justify the opinions of the Federal Trade Commission, which classifies medicine primarily as a business and not as an ethical entity.

If professional societies were to take their moral purposes to heart they would be concerned about the character formation and ethical socialization of their members. Admittedly this would be difficult in a morally pluralistic society where the personal moral beliefs of the members of professional associations can be expected to vary widely. But this is less the case when it comes to the virtues associated medicine as a profession — fidelity to trust, intellectual honesty, courage, benevolence, etc. These are implied by the ends of medicine. If medicine as a profession is to have any unity of purpose these essential virtues ought to be honored. The alternative is to reshape the ends of medicine to suit a variety of purposes other than healing, helping, caring, and sustaining the sick. What those other ends might be is problematic at best and raises questions as to whether medicine would lose its essential character.

The same concern for ethical socialization and professionalization, in the best sense of those terms, applies to medical education. The prime task of medical schools is to prepare new physicians with the skills and knowledge that would make them safe and competent practitioners after graduation. This in a significant degree implies some conscious shaping of the character of medical students so that they will exhibit, then as students, and later as practitioners, those virtues entailed by the idea of a profession.

Medical students usually agree that they know which of their classmates they would not trust to treat members of their families. They are aware that the faculty is often uninformed or indulgent about serious character flaws in some of their students. Students are also aware that faculty may treat problems in character lightly or shy away from dealing with the issue for fear of lawsuits or unpleasant encounters with other students or faculty.

These difficulties are not trivial but there is, nonetheless, an obligation to protect society from unsafe or untrustworthy practitioners. Graduation from an American medical school is tantamount to licensure. Society permits a large degree of discretional latitude to medical educators in their evaluation of students. With this discretionary latitude comes an obligation to protect future patients from patently dishonest or ethically marginal future physicians (14).

This is dangerous territory indeed in which the possibility of abuses of power and injustice are genuine. The difficulties however do not constitute reasons for avoiding the issue. At the very least some effort must be expended to detect the more flagrant disorders of character or personality. Given the growing sophistication of the public in medical matters and the variable state of trust in the profession as a whole, medical schools must confront this obligation or face a narrowing of their freedom as educational institutions.

Summary

There is widespread concern today among conscientious physicians, educators and the general public that medicine is becoming "deprofessionalized," that the profession is losing its commitment to the kind of character traits requisite for protection of the welfare and interests of patients. In the analysis of this concern I distinguished between the idea of profession and professionalization and defined the character traits implied by a genuine act of profession. These important concepts have practical implications for individual physicians, professional societies and medical schools.

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What Medical Students Know about Professionalism

Frederic W. Hafferty, Ph.D.

Abstract

Three different sources of data are used to explore how medical students think about the physician as a professional. The data include exercises employed by the University of Minnesota-School of Medicine to foster professionalism among its medical students, such as the skills of peer review and self-reflection, a 20-hour course for first-year medical students, in which approximately two-thirds of the course focuses directly (e.g., topic-specific readings and class exercises) and indirectly (e.g., medical training and socialization) on the topic of professionalism, and a set of questions asked during admissions interviews which highlight issues of professionalism. Although the data are neither definitive nor generalizable, they do suggest that medical school applicants approach the admissions process well versed in academic and related (e.g., service activities) requirements, but without having given much thought to what it means to be a physician, particularly in terms of professional values. Once in medical school, students express great enthusiasm for "being service oriented" and "doing good" but are not necessarily receptive to the notion that they are obliged in these respects. Instead, students express a variety of utilitarian views on things like codes of ethics and medical oaths to support their stance on nonobligation (sometimes directly and sometimes indirectly). Furthermore, students do not draw distinctions among the values commonly associated with professionalism. In particular, they foresee numerous problems associated with integrating the values of altruism and dutifulness into their future practice of medicine.

Key Words: Professionalism, professional ethics, socialization, altruism, Medical School Objectives Project.

Background

In the fall of 1999, the University of Minnesota-Duluth School of Medicine (SOMD) implemented a new program in professionalism. The program currently contains four exercises (Appendices A–D) and is predicated on several premises. First, the ability and willingness of an occupational group to conduct meaningful peer review, and its practitioners to engage in critical self-reflection, are core to professional status (1 – 7). Second, there is ample historical and sociological evidence to place peer review and self-reflection at the core of any effort to re-invigorate or re-establish medicine's professional status (8, 9). Third, a core objective of both peer review and self-evaluation is to elevate public service above that of self-interest and to promote altruism as a core professional value (10, 11). Fourth, organized medicine has not been successful in establishing an effective system of peer review (12 – 17). Fifth, physicians-in-training are not exposed routinely to the knowledge, skills, and attitudes necessary for the practice of self-reflection nor does medical training provide them with the structural opportunities to do so (18, 19). Finally, much of what medical trainees learn about peer evaluation and self-review is delivered via the hidden rather than the formal curriculum and often is antithetical to the fundamental goals of medical practice (20 – 24).

With these precepts as background, SOMD developed a multi-stage process to formally address issues of professionalism, peer review, and self-reflection. The program is organized around a series of interrelated exercises designed to emphasize how "good doctoring" is linked to the status of medicine as a profession and to its practitioners as professionals. During their first two years of training, students complete four different exercises. These exercises direct students to actively associate individuals (including peers, non-physician role models,

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and themselves) with core professional values and to explain (in writing) their assessments. After each exercise, students receive a detailed report summarizing the responses of their class. In short, each individual exercise is built around: (a) the "doing" of the exercise itself, (b) the receipt and ingestion of the subsequent class report, and (c) the discussions that hopefully take place among students as a consequence of the exercise and/or the report.

The first exercise takes place during orientation. Using a formatted instrument (Appendix A), students are asked to respond to a series of questions (e.g., "Please indicate [by relationship only, i.e., college friend, grade school teacher, cousin,] an individual you personally know whom you would select to be your personal physician"). Following each question stem, students are asked to explain the reasons for their choice. They also are queried about whether any of the qualities they just mentioned might NOT translate well into the current practice environment of medicine, and if not, why not. Four of the question stems used in this exercise (altruism, knowledge, skillfulness, and dutifulness) are drawn from the Medical Student Objectives Project (25). Following this exercise, students receive a report summarizing the overall class responses both in terms of the individuals identified and the reasons for those choices.

The second exercise takes place in the spring of year one (Appendix B). The focus of this exercise is self-review. In this exercise, students are presented with a list of the core professional characteristics they generated (as a class) in the orientation exercise. More specifically, a list was compiled from student responses to the "why" part of each of the ten evaluative stems. In the self-review exercise, students are asked to select three qualities from this list that they feel are relative strengths. They then describe how they think they can draw upon these good qualities and strengths in the upcoming year (to become a better medical student) and how they believe they can draw upon these same qualities and strengths in their future role as a physician. Similarly, students are asked to identify three qualities that they feel are relative weaknesses, how they will work on these qualities/attributes over the coming year to become a better medical student, and separately, how they will work on these qualities/attributes to become a better physician. Following this exercise, students receive a report summarizing class responses.

Appendix A:
Program in Professional Development

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1. Please indicate (by relationship only...i.e., parent, friend, teacher, relative, etc., but with some degree of specificity, "college friend," "grade school teacher," "mother," "cousin") an individual you personally know whom you consider to epitomize the characteristics and personal qualities of someone whom you would select to be **your personal physician.**

Why? Please list the reason or reasons for your choice:

1a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

1b. **Please explain your answer.**

2. Please indicate (by relationship only and someone you know) an individual who just has been accepted to medical school you consider to epitomize the characteristics and personal qualities of an **exemplary medical student.**

Why? Please list the reason or reasons for your choices:

2a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

2b. **Please explain your answer.**

3. Please indicate (by relationship only and someone you know) an individual (not a current physician) you would most like to **be in practice with.**

Why? Please list the reason or reasons for your choices:

3a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

3b. **Please explain your answer.**

4.Please indicate (by relationship only and someone you know) an individual you consider to have extraordinary abilities to work with people of **different social and/or cultural backgrounds.**

Why? Please list the reason or reasons for your choices:

4a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

4b. **Please explain your answer.**

Appendix A: Program in Professional Development

5. Please indicate (by relationship only and someone you know) an individual you consider to be the epitome of an **altruistic person.**
Why? Please list the reason or reasons for your choices:

5a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

5b. **Please explain your answer.**

6. Please indicate (by relationship only and someone you know) an individual you consider to be the epitome of a **knowledgeable person.**
Why? Please list the reason or reasons for your choices:

6a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

6b. **Please explain your answer.**

7. Please indicate (by relationship only and someone you know) an individual you consider to be the epitome of a **skillful person.**
Why? Please list the reason or reasons for your choices:

7a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

7b. **Please explain your answer.**

8. Please indicate (by relationship only and someone you know) an individual you consider to be the epitome of a **dutiful person.**
Why? Please list the reason or reasons for your choices:

8a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

8b. **Please explain your answer.**

9. Please indicate (by relationship only) an individual whom you consider to personify the characteristics and personal qualities of someone who would **NOT make a good physician.**
Why? Please list the reason or reasons for your choices:

9a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? ____Yes ____No

9b. **Please explain your answer.**

10. Please indicate (by relationship only and someone you know) an individual you consider to be the epitome of a **virtuous person.**
Why? Please list the reason or reasons for your choices:

10a. Do you see where any of the qualities you just mentioned might not translate well into the current practice environment of medicine? _____Yes _____No

10b. Please explain your answer.

11. Getting into medical school is a difficult and stressful process. Last year 949 individuals applied for 52 spaces at UMD, a ratio of applicants to acceptees similar to national figures. While everyone wants to put their best foot forward during the application process, there have been instances where individuals fabricated information with the intent of deceiving admissions officers and securing a place in a medical school class.

Please imagine a situation where you become aware of an individual who has lied to get into medical school. Please imagine three such lies. The first lie is so egregious that you would have no problem reporting this individual to an appropriate medical school administrator with the intent that the offending student be dismissed. You consider the second lie to be more equivocal. You find the lie odious and contemptible, but you are not sure it warrants expulsion from medical school. You consider the third lie innocuous, a lie to be sure, but one you consider irrelevant in terms of the one's fundamental character and one's ability to be a good physician.

In the spaces below please provide an example of what you consider to be: (1) an egregious, (2) an equivocal, and (3) a nonconsequential lie

1. Egregious:

2. Equivocal:

3. Nonconsequential:

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*The cover sheet and instruction page are not included in the appendix.

Appendix B:
Program in Professional Development
*Self-Assessment Tool

Class-Generated Standards of Professional Excellence

A. Excellent listener, easy to talk to, good communication skills, personable.

B. Compassionate, caring, kind, gentle, concerned about others.

C. Hard worker, strong work ethic, goal oriented, responsible, does what needs to be done

D. Honest, trustworthy, loyal.

E. Knowledgeable about many different things, breadth and depth of knowledge

F. Tolerant, nonjudgmental, open to everyone, accepts people for who they are.

G. Is a life-long learner, always learning new things, thirst for knowledge.

H. Places the needs of others first, self-sacrificing, gives freely to others, always willing to help (or actually helping) others.

I. Good problem-solving skills, can apply knowledge to solving problems, can put theory to practice.

J. Has deep personal/spiritual convictions/faith, holds strong beliefs and values

K. Organized, punctual, dependable.

L. A perfectionist, meticulous, high attention to detail.

M. Comes from a diverse background/environment. Has lot of experiences dealing with different social/cultural issues, spent time volunteering or working in another country.

N. Does what s/he is told/asked, responsible, faithful.

0. Smart, intelligent, bright.

P. Can fix anything, works well with hands (machines), able to do a variety of things well.

Q. Avid reader, well read

R. Intuitive, insightful

A: First, and drawing solely from the above list, please pick three qualities (aspects of which may be woven across several items) that you feel are **relative strengths** for you.

1\.

2\.

3\.

B. For each of these strengths (independently and in the same order) please write a brief description of how you can draw upon these good qualities **over the upcoming year** in order to become a **better medical student.** Please give your selections and answers careful consideration.

1\.

2\.

3\.

C: Utilizing these same three strengths (once again independently and in the same order) please write a brief description of how you can draw upon these good qualities **in your role as a future physician.** Please give your selections and answers careful consideration.

1\.

2\.

3\.

2

Appendix B: Self-Assessment Tool

D. Second, please identify three qualities that are relative weaknesses for you.

1\.

2\.

3\.

E: Please write a brief description (for each item and in the same order) addressing how you plan to work on these qualities/attributes **over the upcoming year** in order to become **a better medical student.** Please give your selections and answers careful consideration.

1\.

2\.

3\.

F: For these same choices (once again independently and in the same order) please write a brief addressing how you plan to work on these qualities/attributes in order to become **a better physician.** Please give your selections and answers careful consideration.

1\.

2\.

3\.

G: Finally, and with the goal of making this a better tool for future classes, are there **other questions or question stems** (or improvements in general) that you would suggest for future consideration in this exercise (and we would like to note that several prior suggestions have been incorporated into this exercise)?

The cover sheet and instruction page are not included in the appendix.

The third exercise (Appendix C) takes place midway through their second year of training. This exercise focuses on institutional review. In this exercise, students are given the same master list of core qualities and characteristics used in their previous Self-Review Exercise to evaluate how the SOMD attends to, ignores, or even undermines the internalization of these professional qualities. In this exercise, students respond to the entire list of qualities by checking one of three boxes ("Does Formally Address," "Does Not Formally Address," "Undercuts, Counters, or Negates"). Again, students receive a report summarizing the class responses.

The fourth exercise takes place at the end of year two. This exercise focuses on peer review. The exercise is based on many of the same question stems used during the Orientation Exercise (altruism, virtuousness, dutifulness, etc.). Students are asked to identify (by code number) three classmates whom they feel embody the quality under consideration and to explain their choices. The current list of questions covers negative as well as positive qualities (e.g., "Please indicate [by code number only] three classmates whom you would most NOT like to have as your personal physician"). A summary report also accompanies this exercise.

Several caveats help frame the data, observations, and conclusions presented below. First, the four exercises outlined above are considered by SOMD to be a formal part of its instructional program. The instruments used are not treated as questionnaires or as a research undertaking. For example, individual question stems have been (and will be) altered, dropped, and/or added as needed, given the goals of the program. Furthermore, the stems used in the self and institutional review are drawn directly from the orientation responses and thus change every year. In addition, the overall program itself is under constant review with an eye toward modification. For example, following a request by one student, we are exploring how to develop computer-based evaluations in order that individual students can request an evaluation from their classmates along self-selected professional qualities.

Second, although the professionalism program is required to matriculate, it is not a part of any formal course. It therefore lacks any of the traditional structures formally associated with courses and coursework, such as sanctions for noncompletion (e.g., a failing or "incomplete" grade). In this respect, one goal of this program is to gain insights into how learning activities based outside the formal curriculum can be institutionalized.

Third, the fact that UMD is a two-year program influences the kind and content of instruments developed to date. For example, we have not designed any exercises that might be used with more clinical sights of training (e.g., clerkship or residency). Furthermore, we are not convinced that any of the above instruments can seamlessly capture what occurs during, and/or because of, clinical training.

Fourth, all responses at SOMD are anonymous and confidential. Although the exercises are required, the practice of review (self, peer, and/or otherwise "external" sources of review) remains a contentious exercise within medical circles. The rise of managed care, particularly within the for-profit sector, has heightened concerns about things like performance review, compensation, job security, and professionalism. In recent years, medicine has turned to other industries (aviation being a prominent example) for insights into how to encourage performance review (26, 27). Nonetheless, the competing demands of oversight versus anonymity and "blame" versus remediation continue to stir deep passions within medical circles. Fear of "self-incrimination," along with traditional methods for defining and handling mistakes in medicine, directly impact on the ability and willingness of medical professionals to participate in peer and self-evaluation (28–30). The recent Institute of Medicine study on medical errors concludes that the source of most errors in medicine is structural and systemic rather than practitioner based (31). Although this focus (and conclusion) is reflected in our exercise on Institutional Review, issues of agency (and thus, peer review) are a critical part of any social action (including work). Thus, our belief is that issues of professionalism must lie across the domains of structure and action.

Fifth, the program is in its second year of operation. The current second-year class was the first to undertake the Orientation Exercise. This class also has completed the Self-Review, but has not yet encountered the Institutional or Peer Review Exercises (as of this writing). Meanwhile, the current first-year class has completed the Orientation Exercise, but none of the others. In short, the neophyte status of this program limits the data we can draw upon at this time.

Sixth, although the Professionalism Project functions outside the formal curriculum, appre-

Appendix C:
Program in Professional Development
Curriculum Assessment Tool

Class-based Standards of Professional Excellence

		Does Formally Address	Does not Formally Address	Undercuts, Counters, or Negates
A.	Has deep personal/spiritual convictions, holds strong beliefs and values regardless of the consequences	☐	☐	☐
B.	Hard worker, strong work ethic, goal oriented	☐	☐	☐
C.	Self-sacrificing, places the needs of others first, gives freely to others, always willing to help (or actually helping) others, works to make the world a better place	☐	☐	☐
D.	Knowledgeable about many different things, breadth and depth of knowledge	☐	☐	☐
E.	Excellent listener, easy to talk to, good communication skills, personable	☐	☐	☐
F.	Organized, punctual, dependable, reliable	☐	☐	☐
G.	Open to everyone, nonjudgmental, tolerant, accepts people for who they are	☐	☐	☐
H.	Can fix anything, works well with hands (machines), able to do a variety of things well	☐	☐	☐
I.	Compassionate, caring, concerned with the well-being of others, kind, gentle, loving	☐	☐	☐
J.	Comes from a diverse background/environment, has lot of experiences dealing with different social/cultural issues, spent time volunteering or working in another country	☐	☐	☐
K.	Intelligent, bright, smart, intuitive	☐	☐	☐
L.	Avid reader, well read	☐	☐	☐
M.	A perfectionist, meticulous, highly committed to what s/he does	☐	☐	☐
N.	Honest, trustworthy, responsible, loyal	☐	☐	☐
O.	Good problem-solving skills, can apply knowledge to solving problems, can put theory to practice	☐	☐	☐
P.	Does what s/he is told/asked, responsible, faithful	☐	☐	☐
Q.	Is a life-long learner, always learning new things, thirst for knowledge	☐	☐	☐

Part Two:

1. From the list of Standards you checked as being positively influenced at UMD, please select one you feel is being handled particularly well, and in the space below describe how this is being accomplished.

2. From the list of Standards you checked as not being addressed at UMD, please select one and indicate how it could be incorporated into the overall UMD experience.

3 From the list of Standards you checked as being undercut, undermined, or negated, please select one you feel to be particularly troublesome, and in the space below describe what is going wrong.

The cover sheet and instruction page are not included in the appendix.

ciable time within a formal course (offered at the beginning of year one) is now being devoted to issues of professionalism. In this class, presentations, readings, and class discussion target issues of service, altruism, social obligations and responsibilities, and issues of truthfulness and veracity in the admissions process (the latter topic in association with information culled from the last question of the orientation exercise). Observations drawn from these class-based discussions are included in this paper, as are responses from three questions nonsystematically being asked for the first time by the author during admissions interviews ("What does it mean to be a professional?" "What does it mean to act altruistically?" and "What does it mean to have a fiduciary orientation toward one's patients?").

Finally, the four exercises described above are hardly the final (or full) word on peer and/or self-review, or on educational approaches to professionalism in general. There are a number of alternative approaches to professionalism described in the medical education literature, many with features quite different from what is employed at SOMD (2, 32–35).

Core Themes

Three years ago, in a class devoted to a broad look at the physician-patient relationship, I decided to ask my first-year students to read an article by Eckenfels (36). My intent was to pull together some of his key points about community service and use them to generate class discussion.

I began by writing the word "obligation" on the board. I anticipated a moderate amount of discussion following which I would introduce a couple of additional concepts from the article and then move on to some prepared materials on "good" and "bad" patients. Instead, what ensued was a two-hour discussion (even to the point of talking through the class break) during which students raised a number of arguments I had not anticipated hearing. The following year, I again assigned the article and again wrote the word "Obligation" on the board. Again, there was a lengthy and somewhat disturbing (to me) discussion. This past year, I repeated the exercise, but did so having changed the overall focus of the course from a broader sociological look at medicine to one that emphasized issues of professionalism. This re-focusing allowed me to devote additional class time (three class sessions, for a total of six hours) to issues of professionalism, supplemented by readings and related materials. The outline below is a summary of these three class discussions.

Students were quite open about their convictions and opinions, but much of what they had to say did not resonate with what I had long thought of as core to professional status and professional identity. In short, I found myself quite unsettled during these sessions. Not only were the arguments "foreign," but much of what the students said was unaccompanied by any reservations or sense of embarrassment. Either they did not know what it meant to be a professional (at least as framed within the medical and sociological literatures) or they did not hold to those beliefs and values.

So, what did my students say?

Most clearly and emphatically, they rejected the notion that they were obliged to do anything. Period. Although students raised (and in a countervailing way) arguments of altruism and service, the prevailing voice was that students fully intended to do good work and to be caring and compassionate physicians, but that they would do so on their own terms. Where they worked, with whom they worked, the amount of time they worked, what kind of medicine they practiced, etc., were set by personal conviction and desire, and not out of any sense of societal obligation, social contract, or a broader professional "ethic." Much of the content and tone of these discussions reminded me of the philosopher William F. May's term "the conceit of philanthropy" (37). Students certainly verbalized a commitment to doing good, but they were unremittingly clear that the who, what, when, where, and why would remain under the control of the "do gooder."

As a second, and related, value, students repeatedly expressed a need to have "balance" in their lives, with balance being framed in terms of a "responsibility" to: (a) personal, (b) spousal, and (c) family needs. These arguments of responsibility to others (including the self — see directly below) evoked a curious tension for me. I grew up in a physician family. My father was a "GP" (general practitioner), as was my uncle who lived across the street and had his office in his home. Both died at work — literally. My father died at home one Saturday morning following hospital rounds and my uncle died in the hospital while seeing patients. Growing up, I saw my father twice a week; on Wednesday nights before he and my mother went out to dinner and on Sunday afternoons. Otherwise, he was working. My uncle held to a similar schedule. In short, I found myself quite empathetic to what students had to say about meeting "family responsibilities." At the same time, I wondered about the supposedly core values of service and altruism I had encountered so often in the medical literature. Where had they gone? For example, there was little support among my students for Swick's (7) first element in his core definition of professionalism ("Physicians subordinate their own interests to the interest of others"). "Subordination," it turned out, was related to the same negative status as "obligation."

A third — and related — theme expressed by students was the notion that "one has to take care of oneself before one can take care of others." This was a "self-health" and "self-help" argument in which the ability to aid others, students claimed, was directly tied to — and dependent on — the health (physical, mental, and spiritual) of the giver.

Another theme verbalized by students (this time more indirectly than directly) was that all principles reside within the individual. Ethics begins and ends at the level of the individual. One acts ethically because one is good. Although students recognized that professional organizations enact codes of ethics or specify principles of professional behavior, it was equally clear that students did not perceive themselves to be obligated by these standards, particularly in the case where a standard might be perceived to run counter to one's personal values or one's personal sense of responsibilities to self or loved ones. In other words, while professional standards might exist, students did not see them as compelling, nor did they command (either prescriptively or proscriptively) allegiance. At best they might function as "markers" or guidelines. They did not represent an overarching value "orientation" or ethical mandate. Unfortunately, there were no class discussions about the origin of personal values or the relationship of personal values to broader societal norms.

Professional oaths that called upon one to act in a certain way or to adhere to certain professional values essentially were viewed as nonbinding, and were considered so for several reasons. First, oaths or codes were perceived as vague to the point of meaninglessness. They compel nothing because nothing truly is specified. Second, adherence is meaningless because there are no meaningful sanctions. In one of the class discussions, students contrasted medical oaths with oaths taken for other organizations such as the military, scouting, or 4H training. Students could (and did) recite their scouting oath or 4H oath, but had difficulty recalling the content of the Honors Code they had signed two weeks before. More notable, and once again, students pointed out that these other oaths came with sanctions. They meant something. Correspondingly, medicine had few if any sanctions if one failed, for example, to be altruistic. This "void" (with respect to sanctions), students felt, was evidence that the quality or characteristic in question really was not valued all that highly, or that the standard or "bar" was so low as to be totally undemanding.

Finally, students claimed that all of "this" (oaths and standards) was too little and too late. As one student insisted, they already had been admitted to medical school and nobody had told them they were going to have to swear allegiance to a set of beliefs or action guidelines. In response to a direct question from me on this score (asking for a show of hands), only three of our fifty-two students indicated that they had inquired in any manner about whether SOMD would require them to take a professional oath and/or what that oath might entail. For some students, the issue at hand was one of "fairness" (in that they had not agreed to any of this and therefore, it was acceptable to figuratively — or literally — cross their fingers or mumble around whatever phrase, words, or notion they might find disagreeable). Overall, students were suspicious, wary, and rather unrepentant when it came to the topic of oaths. If they did not agree with an oath, they would not take it. Nor would they tell administration that there was a "nonbeliever" in the ranks. It is not that students rejected the notion of principles outright, but what they did reject — in principle — was the notion that anything might be obligatory and that they might be obliged to act or behave in a certain way.

A Hierarchy of Professional Values

Not all professional values generated the same degree of distancing, discontent, or disquietude for students. Answers to the Orientation Exercise were quite telling in this respect. In this exercise, each of the question stems came with a "qualifier" in which students were asked whether any of the qualities they just mentioned might NOT translate well into the current practice environment of medicine, and if not, why not. The qualifier appears below:

Do you see where any of the qualities you just mentioned [meaning just mentioned in response to the "why" part of the overall question] might not translate well into the current practice environment of medicine?

________Yes ________No

If yes, why?

Taken as a whole (see Appendix A), the stems asked each student to identify three individuals:

- they would want as their own personal physician;
- who would make good medical students;
- they would most like to be in practice with;
- who would work well with patients of different social and/or cultural backgrounds;

And who are the epitome of

- altruism,
- knowledgeableness,
- skillfulness,
- dutifulness,
- a virtuous person,

And

- whom they would not like to have as their own personal physician.

Two stems, altruism and dutifulness, have generated, far and away, the largest number of responses to this qualifier. For the Class of 2003, 31 of the 52 students (60%) indicated that they saw possible problems with being altruistic in medicine. For the Class of 2004, this number increased to 38 of the 52 first year class members (73%). The fractions for dutifulness are 50% (26/52) and 46% (24/52), respectively.

Listed below are five examples of direct (and full) quotes from the "Why" part of the altruism stem.

1. Spending so much time helping others can lead to burnout.
2. Altruism is certainly a great quality to have, but it could be taken too far. At some point a person has to take care of him or herself before they can take care of others.
3. I think s/he would quickly be taken advantage of. It is important to have limits in medicine.
4. Being completely selfless at all times can sometimes result in negative consequences for the well-being of that person.
5. You can neglect your own home and family.

Alternatively, being virtuous was not seen to be as problematic by students two weeks into their medical training. Although the "virtuous" item was not the lowest "scoring" stem for either class (that "honor" goes to "cultural sensitivity"), the respective fractions (21% for the class of 2003 and 31% for the class of 2004) indicate that students were more concerned with the "downsides" of being altruistic or dutiful than in being "virtuous."

Examples of responses to the stem about virtue include:

1. You may feel your actions are virtuous but they are crossing guidelines or breaking the law.
2. Moral issues are sometimes not what patients want to hear about.
3. Potentially, it can be difficult to "follow the rules."
4. When an individual's virtues are challenged, some may break.
5. Having a very strict moral code may lead one to be inflexible or judgmental.

Some Corollary Observations

The first time I distributed one of the four instruments to students (a field-tested version of the peer-review instrument: see Appendix D), one student wrote in the margin that s/he was not sure what the term "altruism" meant. Two students wrote a similar note the first time that the Orientation Exercise was administered. This past fall, five students left the altruism question blank — the only question that anybody left unanswered.

Partly to satisfy my curiosity, but partly because I was becoming concerned about altruism and its presence among entering medical students, I began to ask applicants during their medical school interviews (when appropriate, e.g., when an applicant refers to the concepts of professionalism, altruism, or "service orientation" during the interview) one or more of the following three questions:

1. What does it mean to be a professional?
2. What does it mean to act altruistically?

Appendix D:
Program in Professional Development
*Peer Evaluation Tool

1. Please indicate (by number only) three classmates whom you would most like to have as your personal physician.

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

2. In your opinion (by number only), which three classmates will most likely **score the highest on USMLE Part I**.

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

3. Please indicate (by number only) three classmates you would most like to be in **practice with.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

4. Please indicate (by number only) three classmates you feel are best able to work with **patients of different social and/or cultural backgrounds.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

5. Please indicate (by number only) the three classmates you consider to be the most **altruistic.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

6. Please indicate (by number only) the three classmates you consider to be the most **knowledgeable.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

7. Please indicate (by number only) the three classmates you consider to be the most **skillful.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

8. Please indicate (by number only) the three classmates you consider to be the most **dutiful.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

9. Please indicate (by number only) the three classmates you would select to **assume decision-making powers for you** if you were unable to make them yourself (i.e., as in the case of an advanced directive/living will/personal affairs).

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

10. Please indicate (by number only) the three classmates you consider to be the most **virtuous.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

11. Please indicate (by number only) the three classmates whom you would most **NOT** like to have as your **personal physician.**

____(Record # here)
____(Record # here)
____(Record # here)

Why? Please list the reasons or reasons for your choices:

Appendix D: Peer Evaluation Tool

12. Having thought about the above characteristics and attributes, please take a moment to describe (in a sentence or two) your image of the **ideal physician.**

13. Roughly speaking, what percentage of your classmates do you know well?

14. Finally, and with the goal of making this a better tool for future classes, are there **other questions or question stems** (or improvements in general) that you would suggest for future consideration in this exercise? As an example, Question #11 (above) was generated based on comments and suggestions from your preceding class.

*The cover sheet and instruction page are not included in the appendix.

3. What does it mean to have a fiduciary orientation toward one's patients?

To date, I have interviewed seventeen applicants. Twelve were asked at least two of the above questions. For the most part, applicants have little difficulty articulating what they mean by the term "professional." Most often, they touch upon how a physician should (normatively speaking) be up-to-date about diseases and diagnoses, and thus, technically speaking, be able to help people. Much less frequent, but still notable, is some mention of what might be termed "etiquette," or what sociologists refer to as one's "presentation of self." Here, students verbalize that physicians have an obligation (note the reference to "being obliged") to act and/or look the part of a doctor and/or to "listen to their patients" and to "be kind." Only one student explicitly linked the notion of altruism to that of ethics and service. This student alone answered the question definitionally, in that s/he invoked a class taken in college and provided a three-part definition centering around: (a) possession of an esoteric body of knowledge, (b) exemption from external review, and (c) possession of a code of ethics.

The altruism and fiduciary questions, however, gave applicants considerable pause. About half the applicants thus far have admitted that they did not recognize the term "altruism" (or "altruistic"). For "fiduciary," the "count" was even lower, with only one student acknowledging that s/he knew the term in the context of the above question.

In summary, my current mind set, as an admissions interviewer, is that most medical school applicants sincerely want to be physicians, and most have done all the right things to make their applications "worthy." However, most have no fundamental understanding of what it means to be a physician, at least in terms of what medicine says constitute its core professional values.

In the face of these experiences (class discussions, exercises, and interviews), I have begun to wonder, as a sociologist, if these core values actually exist. This is not to say that terms like "professional" (and related core values) are not to be found in the medical literature. Even the most casual scanning of journals such as *Academic Medicine*, *JAMA*, or *the New England Journal of Medicine* will provide ample illustrations. Nonetheless, speaking to the choir may not be the same thing as informing the public about what medicine sees as core to its work, particularly when that public includes future medical student applicants. My experiences to date — as unsystematic and potentially nonrepresentative as they are — have left me with a lurking suspicion that organized medicine is not "getting the word out," be that to pre-med advisors, pre-med clubs, applicants, or the general public. Instead, I find it much easier to imagine advisors and clubs talking about other things, such as how to strategize the interview, scope out what questions might be asked (see www.interviewfeedback.com; www.premedical. com), or "buff" one's application forms (38). Students certainly are being encouraged (formally and informally) to take MCAT "prep" courses (where issues of professionalism are not on the "remedial" docket) (23). Hundreds of hours and thousands of dollars (per applicant) are being spent on "remediation" and "enhancement," but precious little, if any, time is being spent exploring issues of responsibility, commitment, and obligation. In short, little effort is being expended on exploring what it means to be a physician — at least in terms of how medicine claims, in academic medical journals, to reside as the core of physicianhood.

All this brings us to a core point. What is said "internally" by organized medicine about what it means to be a physician, and what is said "externally" may be two different things. Medicine may claim that it is being consistent, but if we focus on behavior (and here we can include the behavior of applicants, students, faculty [via their teaching responsibilities] and accrediting bodies), issues of knowledge and skills clearly rank far above those of values and attitudes. Kaplan Inc. (widely known as "Stanley Kaplan") does not offer remedial work in professionalism, nor does it offer to place students in community service activities or to heighten their "altruism score." Review courses for the United States Medical Licensing Examinations (USMLE) have a similar (and equally restricted) focus. When applicants look for "an edge" they focus their energies on what medical schools "say" is important, not in the rhetoric of AAMC press releases or medical school mission statements, but in terms of how medical schools "behave" when they go about the work of teaching — and, more important, evaluating — their students. It is true that organizations within medicine (the Association of American Medical Colleges [AAMC's] "Medical School Objectives Project [MSOP] Report" (25) and the American Board of Internal Medicine's "Project Professionalism") (39) are working to promote professional values. Nonetheless, the fact remains (again in terms of organizational behavior) that none of these efforts have produced "responses" in the for-profit sector (e.g., Kaplan). Thus, trainees continue to view these values (and rightly so) as peripheral and/or nonessential. With all that is good — and potentially corrupting — about capitalism, you can rest assured that if medical schools were serious about identifying "altruism" and/or "virtuousness" as core to their educational mission and socialization processes, then companies like Kaplan would develop programs to "maximize" these qualities (along with measures to validate their claims that they are doing so).

Conclusions

In the beginning of this paper, I raised two questions. First, what do medical students "know" about professionalism? The answer, I believe, is "not a great deal." Moreover, I do not believe — at the current time anyway — that medicine has had a great deal to say to medical school applicants about what it means to be a professional, be that at the undergraduate college level or at the outset of their medical school training. White Coat Ceremonies most certainly exist, but if SOMD students are at all representative of the applicant pool and general medical student body, then the emphasis on humanism and the symbolism of the white coat remain buried beneath values such as "balance" (rather than "sacrifice"), the belief that ethical mandates reside within individuals (rather than professional groups), and a rather resounding rejection of "obligation" in favor of William F. May's "conceit of philanthropy."

These are not encouraging signs.

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Professionalism in the Practice of Medicine

Samuel W. Bloom, Ph.D.

Abstract

Although medicine is universally recognized as the archetype of the professions, it can only be understood as part of the modern medical center, a dynamic social system consisting of the university, the hospital, the medical center and, most recently, corporate managed care. Such a view results in a portrait of medicine as a profession transformed, driven by huge and growing health care markets, its fate tied not only to state bureaucracies, but also to the dynamics of both health and non-health care businesses. The question asked here is how does such a radical change in medical practice affect medical education. Using methods of historical analysis, it appears that medical educators operate as though the educational process itself determines the values, and therefore the present and future behavior of their students. In other words, at the end of their formal education, doctors are fully formed professionals. However, from the analysis of this paper it can be concluded that the physician as an individual cannot function independently of the structure of the society and its general conception of the world. In the structure of medicine's present situation, the ethical standards of professionalism, as they are classically defined, cannot survive. Instead, modern medical graduates, much like their teachers and professional mentors, will be forced to adapt to a situation that is contradictory to the best traditions of medicine. How to stop this process is the urgent question. Three answers are presented.

Key Words: Professionalism, medical education, medical center, socialization for the profession, managed care.

PROFESSIONALISM has both precise and common usage definitions. It is easy to place medicine within the precise framework because it is universally recognized as the archetype, or epitome, of professionalism. Yet, to understand medicine in the full contours of its professional identity, it is necessary to see it in relation to several major institutions, especially the university, the hospital, the medical center, and most recently, corporate managed care. However, these are only the major structural components of medicine. How then can the implications of professionalism be incorporated into the process of medical education? To do so, in my view, requires a historical perspective which places medicine in the modern medical center, as a dynamic social system. What emerges is that medicine as a profession has been transformed and driven by huge and growing health care markets, with its fate tied not only to state bureaucracies but also to the dynamics of both health and non-health care businesses, even to what has been called the transformation of capitalism itself (1).

The question then is, how does such a radical change in medical practice affect medical education? In my experience, medical educators operate as though the educational process itself determines the values, and therefore the present and future behavior of their students. This presumes that the future doctors, armed with the intelligence and personal, humanitarian values that determine their selection and reinforced by the dedication to the best of professionalism in their medical school training, can therefore emerge at the end of formal education as fully formed professionals. As such, they are ready for the marketplace of contemporary practice, able to preserve their professional values against the corruption of contrary forces. My answer to that is encapsulated in Henry Sigerist's warning, seventy years ago, that medicine has been determined (2) "in different peri-

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ods of history, by the structure of the society at the time and by its general conception of the world. . . . The physician's position in society is never determined by the physician himself but by the society he is serving." In other words, the physician, as an individual, cannot expect to function independently of the structure of the situation in which he works. What then are the determinants of professionalism in contemporary society?

The Professions: Defined

Scholars agree that professions developed out of the medieval guilds and universities. The earliest use of the term recorded in the *Oxford English Dictionary* dates from 1541. There is no corresponding term in any language of the ancient world (3, 4). Yet doctors, clergymen, and lawyers, the basic professions of Western society, were part of earlier societies. Today's medical graduates, for example, take the Hippocratic oath, which dates from the fifth century, B.C. (5). Therefore, in any discussion it is necessary to define these and other professions as they now function.

A profession is distinguished from nonprofessional occupations in two fundamental ways. First, it contains an abstract theoretical knowledge base that requires extended formal training. Second, the welfare of the community is enhanced by the professional practitioners. All studies of the professions agree that only those occupations which combine these two qualities in significant measure qualify fully for professional status in our society (6–11). Two other characteristics have long been associated with the professions. First, their practitioners form a distinct social group, classified as such both by the practitioners themselves and by the society in which they operate. The basis of this social group is in their professional activity and not some other social or economic attribute. Second, the social group itself is organized into an association which establishes formal rules and informal practices of behavior. The association subscribes to ethical standards, disciplines its own members, and thus preserves the integrity and independence of its members.

One can elaborate on this definition, but for the purposes at hand, no further elaboration is necessary. Instead, I propose that these two premises, an extended knowledge base and a commitment to function as part of a social contract for the welfare of the community, should be viewed as the hub of a dynamic social system, subject to constant pressure from competing forces in an ever-changing society. I propose further that this social system is guided by dynamic inner requirements to establish and maintain equilibrium, much like other types of systems (12–14).

The medical center is the modern expression of the sum of medicine's relationships as a profession. Briefly, the modern medical center is a conglomerate, bringing together medical institutions of diverse types and functions, under an administration that is unified to some degree, for the common purposes of medical education, medical care and research (15). Historically, Columbia-Presbyterian, in 1928, was the first organization of this type; since then, it has become the dominant model for American medical schools. I will begin by abstracting, in a visual form, a systemic arrangement of the vital components of the medical center as a social system. Such a system (Fig. 1) builds from a relationship between the medical profession (I) and the community (II).

The Medical Profession in Interaction
With The Community It Serves
(I)
Medical Profession
Community
(II)

Fig. 1. The medical profession in interaction with the community it serves.

Fig. 2 illustrates the distinguishing characteristics of medicine as a profession. Knowledge and its application serve as the roots of the profession, and are the natural source for quite different behavioral modes. This is illustrated in Fig. 3. Knowledge forms an axis with the cognitive-rational mode whereas the application of this knowledge serves as the active-affective axis (Fig. 3).

The medical center is the site at which three main functions, teaching, research, and clinical service, are presumably coordinated. All of these components can be combined into an octagonal model of the medical center in a state of balanced tension (Fig. 4).

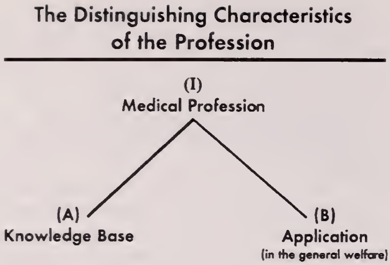
The Distinguishing Characteristics of the Profession
(I)
Medical Profession
(A)
Knowledge Base
(B)
Application
(in the general welfare)

Fig. 2. The distinguishing characteristics of the medical profession.

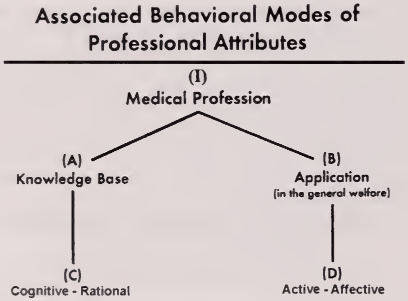
Associated Behavioral Modes of Professional Attributes
(I)
Medical Profession
(A)
Knowledge Base
(B)
Application
(in the general welfare)
(C)
Cognitive - Rational
(D)
Active - Affective

Fig. 3. Associated behavioral modes of professional attributes.

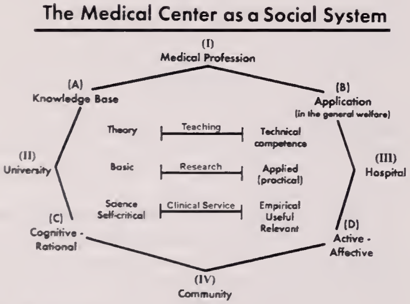
The Medical Center as a Social System
(I)
Medical Profession
(A)
Knowledge Base
(B)
Application
(in the general welfare)
Theory
Teaching
Technical competence
(II)
University
Basic
Research
Applied (practical)
(III)
Hospital
Science Self-critical
Clinical Service
Empirical Useful Relevant
(C)
Cognitive - Rational
(D)
Active - Affective
(IV)
Community

Fig. 4. The medical center as a social system.

I will use this model to illustrate how the separate structures that have developed to fulfill the main functions of medicine are integrated into one balanced form. Specifically, the knowledge base must underpin all aspects of the teaching and research components. The university (II) serves as its main underlying social structure and source of control. We know historically, for example, that when professions have tried to exist entirely outside the university, they have tended toward the vocational, the narrowly practical, and the commercial (16–18). Thus, the university, when it is effective as an institutional base, strongly influences the other axis, and its institutional base, the hospital, to be universal and not particularistic, to be self-corrective and technically valid, and not just utilitarian (3).

The context for this social system is the community in which it exists. This source of influence is never at rest. One can identify how the community has exerted its influence on both the university and hospital together and on each separately (19–21). However, for more than half a century, dating roughly to the beginning of the twentieth century, the community accepted the notion that it was the development of scientific medicine that best served the welfare of society. As a result, there was a long period in which medical institutions, both in their teaching and service aspects, remained insulated in many important respects, from direct influence by the community. The authority of physicians, during this period, was virtually without question. Professional autonomy was at its strongest.

During the two decades from 1960–1980, however, the view of the community was drastically revised and shifted to the service oriented, B to D axis. The development of knowledge which, in the so-called golden age of scientific medicine had been dominant, lost its overwhelming primacy. This is the beginning of what Kenneth Ludmerer, in his landmark study of medical education, calls the second medical revolution of the century (17) "the breaking of the social contract." No one, in my view, could have anticipated the consequences of the signal event from which this revolution emerged, the Medicare and Medicaid acts of 1965. "The clinical activities of medical schools began to hypertrophy, swelling out of proportion to their other duties." Ludmerer wrote, "Clinical services rapidly grew to become their most conspicuous activity and most important source of income. In the process, their link to the university weakened, their commitment to academic values decreased, their tradition of charity eroded, and they became enmeshed more firmly than ever in the health care delivery system."

The paradox is that professionalism, in its purest form, is assumed to be a value construct, which emphasizes the ethical qualities of medicine's social contract. However, the octagonal model in Fig. 4 clearly indicates that it is the institutional structure of the medical center organizations which is the determining variable. The recurring concerns and the resulting programs of educational reform (22), according to this thesis, are based on the clash between ideology (value systems) and social structure (22, 23). As I stated in an earlier paper (23),

> The corporate bureaucracy of the medical school has become an ever-expanding institution, requiring a flow of resources that exceed the income which is available from education itself (tuition, competitive training grant programs, or subsidies, such as Medicare-Medicaid). Thus the medical school is forced to maintain itself indirectly on resources that are allocated to support the goals either of research or of the technology of the specialized tertiary care typical of teaching hospitals. By the very definition of this situation, educational values become subordinate to the requisites of the organizational structure of the medical school, and therefore to policy that is determined by external groups who provide the means and regulate the activities of the major persons within the institution.

Among such groups, managed care has taken the dominant place in the current health care system of the United States. No discussion of medicine today is possible without attention to its transforming effects. According to the American Association of Health Plans (AAHP, the trade organization for HMOs, located at 1129 20th Street NW, Suite 600, Washington, DC 20036) the most recent available figures (as of the end of 1996) estimate that 80% of potential commercial enrollees (or 70% of the total population) are enrolled in managed care programs (24, 25). Managed care is defined as (26): "Health insurance plans intended to reduce unnecessary health care costs through a variety of mechanisms, including: economic incentives for physicians and patients to select less costly forms of care; programs for reviewing the medical necessity of specific services; increased beneficiary cost sharing; controls on inpatient admissions and lengths of stay; the establishment of cost-sharing incentives for outpatient surgery; selective contracting with health care providers; and the intensive management of high-cost health care cases." This definition includes Health Maintenance Organizations (HMOs) and Preferred Provider Organizations (PPOs).

Without question, managed care has radically changed the institutional structure of medicine. Instead of the dominance and autonomy of physicians and voluntary hospitals that had characterized medicine at the beginning of the twentieth century, power has been transferred to the huge health care conglomerates that increasingly represent managed care programs. The irony is that prepaid, capitated medical care for broad-based populations originated in the 1920s and was represented by non-profit organizations like Kaiser-Permanente (1945) and Group Health Cooperative of Puget Sound (1947). The major objectives of these early variants of HMO were to increase access to quality health care at a low price, with a strong emphasis on primary care and prevention. The profit potential of this type of organization, however, after a long intervening period, has more recently attracted the establishment of publicly-traded, for-profit corporations in a marketplace that has grown phenomenally in recent years (25).

The challenge of managed care for medicine as a profession and for medical education specifically is daunting. My octagonal model is, in its present form, obsolete. For-profit managed care, as an institution, threatens to overwhelm the medical center, dominating the whole system. The most pressing question for medical education today is whether it will respond to this challenge by addressing the structural problems of organization, the sources of authority and allocation of resources, the power centers of decision making. Or will the approaches be limited, as they have been so frequently in the past, to calibrations of curriculum that reflect ideology without reference to the realities of institutional structure?

In the definition presented earlier, professional associations were responsible for "maintaining ethical standards that preserve the independence of its members." In medicine today, this function has been overwhelmed by the demands of managed care. The leaders of medical education, in turn, proceed as though the practice of medicine has not changed. They turn their graduates loose after formal training that offers virtually no preparation for the current realities of medical practice, as though scientific and clinical expertise will be enough. In this process, I do not see how the ethical standards of professionalism as we define them here can survive. Instead our graduates will be, like our leading teachers and professionals, forced to adapt to a situation that is contradictory to the best traditions of medicine.

A more thorough analysis of the incongruity of combining the managed care industry for the delivery of high quality medical care with the requirements of ethical medical professionalism has appeared elsewhere (27). It should be clear, nevertheless, from even this superficial analysis of the social system of the modern medical center, that the commodification of health care is a violation of the basic requirements of medicine as a profession. At risk is medicine's centuries-old contract to act as a profession dedicated to the use of its scientific knowledge to serve the general welfare of the community. Without that contract, professionalism is dead.

Within the broader context of the sociological analysis of health care, this discussion fits the pattern associated with Parsons (28), expanded to account for power relationships and the massive change in the social context of medical practice. Put another way, I have described a profession which "possesses power as expressed in social organization, in the way people think about and act regarding health care, as well as its control over medical work itself" (1). The question then asked is, what happens when such a profession is transformed from a situation in which physicians were petty bourgeois entrepreneurs into one in which physicians are part of huge and growing health care markets? One answer leads into the forest of theory, from Weber, Marx, Durkheim and others (1). Here, however, we will ask a more urgent question: what can be done?

The first answer, in my view, is to maintain the standards and values of the key institutional structures which have shaped medicine as a profession. The university, by its nature, does not allow research enterprise to be bought. If the medical school allows its science infrastructure to become part of for-profit industry, the rules of science are violated. Science depends on the freedom to collaborate, to share, and to publish. Science does not fit into the secrecy and the protective rules of business enterprises. This is hardly a novel argument. Fifteen years ago, eloquent and incisive arguments were published in four books, with the same warning (16, 29–31).

Second, clinical medicine must be guided by the rule that any decision made by a physician on behalf of the patient must be based on the available knowledge and evidence. Cost-benefit is not a fundamental guidepost of clinical medicine.

Third, medical education must add reality-preparation for the complex, power-driven competition in the medical marketplace. Health care is a social good. It may even be a social right. It is not a commodity.

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Training Doctors for Professionalism:

Some Lessons from Teaching Clinical Medical Ethics

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Abstract

Medical professionalism encourages physicians to place their patients' interests above self-interest. In recent years, many medical organizations, including the American Board of Internal Medicine (ABIM), Association of American Medical Colleges (AAMC), and the American Medical Association (AMA), have developed initiatives to strengthen medical professionalism. By emphasizing professionalism, supporters of these initiatives hope that medicine and physicians may recapture professional autonomy, decrease public criticism of medicine and physicians, and help physicians regain the moral high ground in the unending struggle with payers, both public and private. One crucial question facing medical educators is whether the concepts of professionalism can be taught to medical students and residents. This paper draws upon the author's thirty years of experience in teaching clinical medical ethics to provide guidance on how to teach the concepts of professionalism to students and residents.

Key Words: Professionalism, medical ethics, physician-patient relationship.

Introduction

ALTHOUGH DISAGREEMENTS PERSIST among experts as to which aspects of medical practice are captured by the term "medical professionalism," in recent years there has nevertheless been widespread agreement within academic medicine that it is essential to teach about medical professionalism to medical students and residents. Before considering whether lessons learned from teaching clinical medical ethics during the past thirty years may be applicable to teaching about medical professionalism, it would be useful to ask why medical professionalism has become the shared theme of many professional groups, such as the American Medical Association (AMA), Association of American Medical Colleges (AAMC) and American Board of Internal Medicine (ABIM), which are not always in accord. There is no simple answer to explain why medical professionalism has rapidly emerged as a unifier for a desperately fragmented profession, but Wynia and colleagues recently suggested (1) that medical professionalism, which in their view consists of "devotion to service, profession of values, and negotiation within society . . . ," serves as a bulwark for medicine against two other forces competing to control medicine — market-driven and government-controlled health care.

Papers presented at the 15th Mount Sinai School of Medicine Ethics Conference, "Understanding Professionalism and Its Implications for Medical Education," suggested some of the following reasons to explain the contemporary importance of medical professionalism: (a) it may help physicians (perhaps in alliance with patients) to recapture some degree of autonomy, at least decisional autonomy; (b) it may help to break the cycle of public distrust and disrespect for physicians and medicine; (c) it may help physicians and medicine gain the high moral ground in their ongoing struggle with payers,

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whether such payers be managed care organizations or government; and finally, (d) it may actually contribute to improving the process and outcome of patient care. My own view is that the political, economic, social and clinical struggles to recapture or at least retain important elements of doctor and patient autonomy are being fought on the battlefield of medical professionalism.

Even if there were widespread agreement on the desirability of teaching medical professionalism, some might question whether we as a profession are capable of teaching it. Such skeptics might raise the following two questions:

- Is it possible to teach the elements of professionalism? For example, the American Board of Internal Medicine has identified seven negative behaviors as being violations of professionalism: abuse of power, arrogance, greed, misrepresentation, impairment, lack of conscientiousness, and conflict of interest (2). The Accreditation Council for Graduate Medical Education (ACGME) has identified positive aspects of professionalism, including respect, regard, integrity, and responsiveness to patients and society that supercede self-interest (3). Many of the elements identified by ABIM and by ACGME relate to innate character traits and the virtue of individuals; this raises the ancient issue of whether character and virtue can be taught. (See below in section entitled "What should be taught?").

- Can you teach the values of medical professionalism without changing the internal culture of academic health centers and the entire health system? While many subscribe to the view that professional values are transmitted to physicians by a combination of didactic teaching and role-model mentoring, others including Dr. Ken Ludmerer (4) — and Samuel Bloom (5) — at this conference believe that the development of professional values is influenced by the values inherent in the entire health system.

  Ludmerer recently wrote:

> "...[S]tudies over the past four decades have documented the profound impact of the entire institutional environment of the academic health center on shaping the attitudes, values, beliefs, modes of thought, and behavior of medical students . . . . Formal coursework and mentoring represent only two of the many factors that affect the development of attitudes. An unfriendly institutional culture can easily undermine the well-intentioned efforts of those trying to impart professionalism by means of the curriculum . . . . The greatest challenge in proving the teaching of professionalism is to modify the internal culture of the academic health center so that it better reinforces the values that medical educators wish to impart. At present this represents no small task for the managed care revolution has caused medical schools and teaching hospitals to become much less friendly to patients and students than they were even a few years ago."

My own observations, based on my work as an attending physician at an academic medical center, reinforce Ludmerer's concerns. Recently, I supervised a particularly empathetic and compassionate resident who had admitted ten complex patients in the previous twelve hours, and was tired, irritable, and overwhelmed by her clinical responsibilities. I tried to serve as her teacher and mentor but found myself having less time to teach because I was forced to document patient records so that I could protect myself against possible legal cases of fraud and abuse. Also, many of the patients we care for in our health system are uninsured and, therefore, are often "neglected" medically between acute in-patient hospitalizations. Further, the teaching hospital I work at faces serious financial constraints, some of which have required the firing of nurses and other patient-care personnel, thereby adding new tasks to those of the already overworked residents. As Ludmerer suggests, it is not easy to model and teach medical professionalism in such a system, a commercial atmosphere which he says (4) " . . . does little to validate the altruism and idealism that students typically bring with them to the study of medicine."

Can the Teaching of Medical Ethics Provide Any Guidance for Developing Teaching of Medical Professionalism?

Cautionary Observations

Although medical ethics has been taught in most American medical schools since the 1970s, there is little data to document whether such ethics training has been successful in improving patient care or patient outcomes, whether the doctor-patient relationship has been strengthened, or whether improvements have occurred in the way medical decisions are reached. Very few studies, if any, have examined the impact on the quality of patient care of teaching medical ethics or of medical ethics in general. For example, one major study showed that despite medical ethics' preoccupation for thirty years with end-of-life issues, the care dying patients receive in American hospitals is inadequate both clinically, because it fails to provide sufficient pain medication and ethically, because it fails to respect the wishes of dying patients (6). Professor Leon Kass, one of the founders of the American bioethics movement, recently commented critically about the achievements of bioethics (7): "Though originally intended to improve our deeds, the practice of ethics, if truth be told, has at best improved our speech." As we move forward to develop and implement a national effort to teach medical professionalism, one lesson to be learned from teaching medical ethics relates to the failure of medical ethics to document its achievements. This suggests that in developing teaching in medical professionalism, it is essential to specify the goals of such new teaching, to demonstrate how such teaching improves the process and outcome of patient care, and to develop from the outset methods to evaluate its impact on students (8).

Positive Guidance

Based on my experience from teaching medical ethics for thirty years, I suggest that any new teaching program (for example, a program in medical professionalism) answers the five questions noted in Table 1.

I will discuss these five questions primarily in terms of clinical medical ethics and will provide tentative answers that I have arrived at with my colleagues, Edmund Pellegrino and Peter Singer (9). Whether our observations about clinical medical ethics also apply to the teaching of medical professionalism is a question I will leave for those with greater expertise than mine in the field of medical professionalism.

TABLE 1
Teaching Clinical Medical Ethics to Medical Students and Residents

1. Why teach?
2. When to teach?
3. What should be taught?
4. How should it be taught?
5. Who should teach?

1. Why teach clinical medical ethics?

There are three important reasons for teaching clinical medical ethics:

- To provide students with essential and practical knowledge about issues that arise frequently when caring for patients and with which students must be familiar in order to provide good care. Such issues include, but are not limited to, informed consent, truth-telling, confidentiality, human subject protection in research trials, and end-of-life care.
- To encourage students to build upon this foundation of clinical medical ethics through life-long learning.
- To introduce students to the central importance of the physician-patient relationship and the ways in which communication occurs and decisions are reached within this relationship.

The fundamental justification for teaching clinical medical ethics (or for that matter, any medical school or residency subject) is based on its contribution to the care of patients. Therefore, the principal goal of teaching clinical ethics is to improve the quality of patient care in terms of both the process and outcome of care. If young physicians are equipped with the skills required to reach ethical decisions regarding patients, their patients will be protected from violations of their dignity. This means that in educating young physicians emphasis must be placed not only on the ethics of the actual decision but also on the ethics of the decision-making process. The skills of ethical analysis are part of the competence-set of young physicians and are a necessary complement to the physicians' knowledge base and competence in the scientific and technical aspects of clinical medicine.

Many of the reasons offered for teaching clinical medical ethics could also be applied to teaching professionalism.

2. When to teach clinical medical ethics?

If clinical medical ethics (or professionalism) is essential to medical education and practice, it should not only be taught as a block course (although some basic instruction is required) but it should also be continuously integrated into the young physician's education at all levels of medical school and residency training. Whenever possible, ethics teaching should be coordinated with students' other learning objectives. For example, an ideal time to teach about brain death and the vegetative state would be during a basic science course on neuroanatomy and neurophysiology. Similarly, the introductory anatomy course offers a unique opportunity to deal with issues of death, dying and respect for the dead body. The course on history taking and physical diagnosis is the optimal time to engage students on topics such as the doctor-patient relationship, truth-telling, confidentiality and informed consent.

Whatever foundational instruction is provided in clinical medical ethics during the first two years of medical school must be reinforced during the clinical years. This point was stated eloquently in 1902 by William Osler in a speech to the New York Academy of Medicine (10).

> "In what may be called the natural method of teaching, the student begins with the patient, continues with the patient, and ends his study with the patient, using books and lectures as tools, as means to an end . . . . . For the junior student in medicine and surgery it is a safe rule to have no teaching without a patient for a text, and the best teaching is that taught by the patient himself."

In the contemporary context, clinical teaching about ethics and professionalism is best accomplished by integrating the teaching into each of the students' clinical clerkships. This practice disrupts the pattern of clinical education least, takes advantage of the students' involvement with actual cases, and eliminates the problem of designing a course to cover all the major ethical and professional issues encountered in all major specialties.

3. What should be taught?

Ideally, teaching about clinical medical ethics should include three dimensions: cognitive skills (information and facts); behavioral skills; and character development and virtue.

a. Cognitive skills. Students should be introduced to the literature of clinical ethics, to the research methodologies used in ethics, and to a practical approach for doing ethical analysis. The specific curriculum should reflect the incidence and prevalence of clinical situations that are encountered in the students' or residents' work. Curriculum design also can be based upon published studies of the epidemiology of ethical dilemmas that are seen in inpatient settings, outpatient setting, or consultation setting. Another approach to curriculum design is to target teaching to meet the perceived needs and preferences of students, which will vary depending on students' and residents' levels of training and specialties (11).

b. Behavioral skills. The assimilation and mastery of cognitive knowledge are not an end in itself for clinicians. To be effective in caring for patients, clinicians must have the behavioral skills that are necessary to put their knowledge to work in everyday clinical encounters. A physician who knows the legal and ethical requirements of writing an order not to resuscitate (DNR) should also be expected to know how and when to initiate discussions about DNR status with patients and families in a thoughtful and sensitive manner. Instruction in the behavioral skills of clinical ethics requires teaching and role modeling by experienced clinicians who can demonstrate the skills in practice. It further requires that students have the opportunity to practice these skills while being supervised by experienced clinicians.

An eloquent argument for integrating cognitive knowledge and behavioral skills is contained in an influential consensus statement (12) which concluded that students should be taught both cognitive knowledge and "interactional abilities to deal successfully with most of the moral issues they confront in their daily practice."

c. Character development. Ten years ago, in discussing the importance of character development as part of medical ethics teaching, my colleagues and I wrote the following statement, which may apply with equal force to the current goals of teaching medical professionalism (11):

> In addition to cognitive knowledge and behavioral skills, some attention must be paid to the affective component of clinical ethics — that is to say, to the kind of person the physician should be as well as the kind of decisions he or she should make. In short, ethics requires that the physician be a person of character, one who can be expected habit-

> ually to act in the patient's interests when no one is watching. Trust is essential in the healing relationship. The norms and principles of clinical ethics must in the end be filtered through the person of the physician. The values or principles the physician chooses, the theory of ethics he espouses and the way he interprets the relationship with the patient will shape the ethical decision he makes in a given case. In order for a physician to perform in an ethically defensible way, both procedurally and substantively, some development of his character is essential. This is the most difficult task in clinical ethics.

A statement such as this inevitably raises the question that Plato raised in "The Meno" (13): "Can you tell me Socrates: Can virtue be taught? Or, if not, does it come by practice? Or does it come neither by practice nor by teaching, but do people get it by nature, or in some other way?"

4. How should clinical medical ethics be taught?

At the University of Chicago we emphasize the following six principles (the "Six C's") in teaching clinical medical ethics (Table 2):

I wish to elaborate here on the fifth point — that clinical medical ethics teaching should be clean (i.e., not too complex). Our model for teaching clinical medical ethics includes cognitive training in the fundamentals of ethics, with a core set of lectures on 8 – 10 important topics; a recommended text that is clinically oriented; and a basic approach to ethical decision making (11). It also provides students with a bibliography of accessible articles and reference materials for further reading. The students are also provided with opportunities to develop behavioral skills in their clinical work ("See one, do one, teach one"). For example, after reading about the core elements of informed consent, a student observes a skilled clinician negotiating consent with a patient, and the student is then given an opportunity to elicit informed consent while the instructor observes the student-patient interaction.

TABLE 2
Principles for Teaching Clinical Ethics
The 6 C's

1. Clinically based
2. Cases (real)
3. Continuous
4. Coordinated (integrated)
5. Clean (i.e., simple)
6. Clinicians as instructors

5. Who should teach clinical medical ethics?

Medical ethics should be taught by those who do it well and who have the capacity to motivate students and residents to improve the quality of their patient-physician interactions and patient outcomes. These teachers could be either practicing physicians who have received training in ethics or bioethicists who have clinical experience. Role-model-teaching physicians are especially important for the following reasons:

- Physicians can teach ethics in the clinical setting by referring to actual clinical cases, as is done in most other effective clinical teaching.
- Physicians are responsible for resolving — rather than just for analyzing — clinical-ethical problems in order to reach good decisions with their patients.
- Physicians also demonstrate ethically appropriate professional attitudes and values to students so that students learn both from the formal teaching of clinical ethics and from their teachers' modeling of ethical behavior and professional conduct.
- Physician-teachers incorporate clinical-ethical considerations into the routine practice and teaching of medicine.

The five questions that have been addressed with respect to teaching clinical ethics should also be considered when developing a teaching and training program in medical professionalism. I suspect that many of the issues addressed about clinical medical ethics would apply also to teaching medical professionalism.

Two Final Thoughts on Teaching Clinical Medical Ethics and Medical Professionalism

Can Character Be Taught?

This ancient question has no easy answer. In my view, medical education and training not only provides students with a new vocabulary and a new knowledge base, but also serves as a moral pilgrimage in which character and attitudes are molded by the experience of caring for sick patients. While most students will change during training, not every student will emerge with a set of character traits that ensures that ethical and professional standards are always maintained. This, in turn, places a heavy burden on those who help select medical students for admission to medical school. Medical school admissions committees do very well, but sadly, there is no gold standard with which to identify with precision those students whose character flaws may prevent them from developing the kind of ethical and professional attitudes that society wants and demands of its physicians. Left to myself, I would always select students based on positive character traits (if I could identify them) before GPAs or MCAT scores, but I acknowledge that such a selection process is an art, not a science (14).

The Fundamental Importance of the Doctor-Patient Relationship

After undergoing trial by fire during the last decade, the doctor-patient relationship in the US has emerged with renewed vitality and a strong endorsement from patients. This is as it should be, since the doctor-patient relationship has always, at all times, served a universal human need (i.e., helping people who turn to medicine for help) and has pursued an unchanging goal (to provide the best help it can within the scientific limits of the times). The ethics and professionalism of the modern physician is not very different from that of the ancient physician who subscribed to the following Hippocratic guidelines (15): ". . . as to diseases make a habit of two things, to help or at least to do no harm."

Almost 2500 years ago, in a remarkable passage in Book IV of "The Laws," Plato recognized that good doctor-patient relationships were required to achieve the goals of medicine. Plato described inadequate doctor-patient relationships, what he called "slave medicine," as follows (16):

> "The physician never gives the slave any account of his complaints, nor asks for any; he gives some empiric treatment with an air of knowledge in the brusque fashion of a dictator, and then is off in haste to the next ailing slave . . . "

Plato contrasted this inadequate doctor-patient relationship with what he called the physician-patient relationship for free men, in which (16):

> "The physician treats their disease by going into things thoroughly from the beginning in a scientific way and takes the patient and his family into confidence. Thus, he learns something from the patient. He never gives prescriptions until he has won the patient's trust, and when he has done so, he aims to produce complete restoration to health by persuading the patient to comply."

The best clinical medicine, Plato tells us, is practiced when the scientific and technical aspects of care are placed in the context of a personal and professional relationship in which the physician strives to win the patient's support and trust. In this regard, the professional and ethical values described by Plato and those that are expected of the contemporary physicians are remarkably similar. Both are based on a medical relationship with the patient in which the physician's core ethical and professional values are the foundation of good clinical care.

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Professionalism and the Teaching of Clinical Medicine:

Perspectives of Teachers and Students

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Abstract

Principles of medical professionalism include humanistic values, altruism, ethical and moral behavior, and a lifelong commitment to scholarship and learning. These principles can provide behavioral guidelines to residents, fellows and their teacher-physicians during the formative years of postgraduate training. This short paper presents some of the challenging professional questions raised during these years of training, where medical professionalism may help to guide us.

Key Words: Professional competence, physician's role, medical education, physician-patient relations.

As a practicing academic pulmonary intensivist for the past fifteen years, I have taught clinical medicine to hundreds of residents and fellows at the bedsides of critically ill patients in intensive care units. It is during the residency and fellowship years that "book-smart" medical school graduates mature into fully developed, autonomous physicians. Although they have all graduated medical school and they are all called "doctor," it is not until they take on the role and responsibilities of doctoring that they truly become physicians. Tremendous change and growth occur during these years as a direct result of their hands-on care of a great many patients, under the supervision of experienced teacher-physicians.

High-quality clinical medicine and its teaching require consistent guidelines on how to behave as a physician and a clear vision of what one is trying to accomplish — in addition to the knowledge, skills and tools of science and medicine. In other words, we need a road map and a destination, for "If we don't know where we are going, then it doesn't really matter which road we take" (to paraphrase the Cheshire Cat from *Alice in Wonderland*) (1). For these behavioral guidelines, we look to the essential principles of medical professionalism, such as humanistic values, altruism, ethical and moral behavior, and a lifelong commitment to scholarship and learning (2, 3).

The way we clinician-teachers conduct our own lives has a lasting effect on our trainees, since they look to us and how we behave for lessons on how to actually be a doctor. During these formative years, trainees and teachers develop strong bonds that often span entire careers. An essential part of the teaching of clinical medicine is role modeling — with trainees learning by example how to interact with patients, how to function as physicians and how to comport themselves as physicians on a day-to-day basis (4). And, as you might expect, they ask us many questions, both explicitly and implicitly. How do we ethically justify the "high-wire act" of allowing inexperienced students to practice on the vulnerable sick, knowing that mistakes might occur? The protection of our patients from harm must always be kept in mind. How do we simultaneously allow auton-

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omy and yet retain supervision — recognizing that doctors cannot learn to be decisive and accountable without the freedom to make decisions, to sometimes be wrong, and to learn from mistakes? Physicians must make scores of decisions daily, both large and small. I believe it is absolutely vital that my students develop the ability to make decisions, and to fully accept responsibility for the results of the decisions they have made.

How do physicians relate to each other and to society as a whole? What is our responsibility to the larger world? How do we balance practicing selflessly and making a living? What powers does our society invest us with, and what are the responsibilities that go along with these powers? What is the historical role of physicians in our society, how has that changed, and where is it going? These are all difficult, challenging questions, with continuously evolving answers.

Recent pressures on academic clinical-teachers have challenged our own abilities to best represent medical professionalism. Foremost is the conflict between medicine as a business and medicine as a profession (5). Academic medicine is in turmoil as a result of changes in health care reimbursement. The managed care industry does not include the costs of postgraduate training of physicians as part of their responsibility and, therefore, refuses to pay for it. Government-mandated patient-record documentation requirements for medical school faculty have become progressively onerous, leading to more writing on charts and less supervising and teaching. Fiscal pressures have forced clinicians to see increased numbers of patients in order to maintain solvency, thereby eroding the time available for the thoughtful education of trainees. Time for precious contemplative thought, study and research has dwindled.

A second area of conflict is the relationship between academic medicine and the pharmaceutical industry (6). We try hard to teach trainees to be independent of industrial pressures and involvements which may influence their treatment choices. At the same time, industry is a major source of research funding for faculty at medical schools. Juggling these two often-conflicting agendas can be quite challenging.

A third area of tension is in one of the important underpinnings of medical professionalism, the self-policing of our profession — the willingness to admit errors and to report the errors of others. There is enormous conflict between doing this (because it is the right thing to do) and not doing this, for fear of repercussions — both internally from peers, supervisors and program directors, and externally from the malpractice industry and the justifiable fears of being named in the National Data Bank. These are just some of the major problems which test us and test our abilities to represent our profession to our students as we would like to.

American medicine in general and academic medicine in particular are constantly changing, driven by endless experiments in health care financing, new medical discoveries, and evolving societal needs and desires. We cannot plan for the future, since neither we nor our students know what the future will bring. Our responsibility, therefore, as clinical-educators and role models, is to prepare our students for this unforeseen future by providing them with a strong foundation, flexibility and clear sense of purpose. We hope to teach residents and fellows not only "to do things right" but also "to do the right things."

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Teaching Professionalism:

A Student's Perspective

Jennifer Fehser, M.D.

Abstract

As a fourth-year medical student, I was asked to speak about the role of the medical school in teaching and promoting professionalism in its students, and specifically to describe and critique the efficacy of Mount Sinai School of Medicine in this endeavor. I concluded that the concept and framework of professionalism can, in fact, be effectively taught in medical school, but that role modeling and mentoring are also crucial to the development of the professional. Finally, I make suggestions for furthering the promotion of professionalism through medical education at Mount Sinai.

Key Words: Professionalism, professional standards, professional practice, medical ethics, medical education, medical curriculum student's perspective.

For me, a fourth-year medical student, there are several components to professionalism. Aside from the obvious, that a profession "owns" a specialized body of knowledge, there are additional components that distinguish a profession, such as medicine, from other jobs or trades (1, 2). For example, professionalism requires adherence to a high ethical code. It also incorporates a sense of responsibility and public service that is not necessarily inherent in other jobs; physicians are expected to act for the public good and the good of their patients, and to place this good of others above their own interests or the interests of the profession (1, 2). Other qualities that I strongly associate with professionalism include humanism, excellence, accountability, compassion, autonomy, and respect.

Where did I learn this sense of professionalism? Should it — can it — be taught in medical school? In particular, did the Mount Sinai School of Medicine teach it to me? These are the questions that I have been asked to address.

In my view, during the rigorous process of applying to and being accepted by the medical school, the school selects a body of medical students who already exhibit many of the qualities deemed essential for physicians to possess. In my case, I did have a sense that medicine was a calling, as opposed to simply a career. But if you had asked me to define professionalism three and one-half years ago, I am sure that while I had a vague sense of the responsibility and the commitment to service that it entails, I probably would not have been able to articulate it clearly, and I certainly did not understand the true context, history, and significance of the word.

I have found that the formal teaching of the concept of professionalism is a priority here at Mount Sinai. In preparing for this talk, I read a recent article by Dr. Herbert Swick and colleagues in the *Journal of the American Medical Association* (3). The authors surveyed many medical schools to determine if and how they teach professionalism to students. I was surprised to see that, according to this survey and analysis, only 42% of the schools which claimed to teach professionalism specifically addressed the concept that doctors are obligated to respond to societal needs, and only 54% taught students to evince core humanistic values. Mount Sinai strongly emphasizes humanism in medicine and attempts to teach students to respond to societal needs, facts which I had previously taken largely for granted.

Ms. Fehser was a 4th-year medical student when she made her presentation at the conference.

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The major forum through which professionalism is formally taught at Mount Sinai is through the Medical Ethics curriculum, which spans all four years of the medical education. During the first year, one of the major focuses of this curriculum is to define professional responsibility. Students learn that physicians have responsibilities to their patients, to society, to the profession, and to peers, as well as to themselves. Scenarios are presented in which there are conflicts among these different responsibilities and students are asked to consider what they might do. Similarly, the qualities which are essential for physicians to possess — qualities such as compassion, knowledge, and respect — are elicited and discussed. In addition, several codes of ethics, ranging from the Hippocratic Oath to the Code of Maimonides, are examined and discussed thoroughly. As the culmination of these discussions, first-year students take part in the White Coat Ceremony; with the symbolic cloaking of their sparkling new white coats and with their recitation of the Code of Maimonides, students begin to understand and to accept the responsibilities that come with joining the medical profession. In addition to the Medical Ethics curriculum, our dean leads a discussion on professionalism during the third-year retreat, and our chairman of medicine leads a similar discussion during the clerkship in Medicine. Through these many formal and didactic exercises, as well as others, Mount Sinai demonstrates its commitment to teaching and reaffirming the importance of professionalism.

I also think that Mount Sinai does an excellent job of promoting important components of professionalism, such as empathy, humanism, cultural competence, and community service. By fostering these qualities, such as through the Morchand Center for Clinical Competence and the Office for Multicultural Affairs, Mount Sinai will effectively produce professionals.

So, is it through this formal and informal teaching that I learned what professionalism is and the responsibility that it entails? I would argue that while didactics are certainly an important part of the process, they alone are not sufficient (4).

For me, it was largely through the didactic exercises that the concept of professionalism became clearer intellectually, and I began to strive for the ideal. But a major component of my learning "what a professional is" occurred through contact with professionals at the bedside, in the clinic, and in the operating room. For example, late one night when I was on call at a busy affiliate of Mount Sinai, a 47-year-old woman with end-stage breast cancer was admitted to my team's internal medicine service. Her husband and family of ten children had brought her. The woman had been fighting breast cancer for nearly ten years and, at this point, had widely metastatic disease. After examining the woman, who was encephalopathic and in a tremendous amount of pain, and after receiving the results of key tests, we realized that she most likely was not going to survive the night. The scene was incredibly emotional and I found myself fighting back tears. Despite the fact that my resident was being paged relentlessly, a sign of the dozens of other responsibilities he held that night, he chose to sit and listen to the dying patient's husband for nearly an hour, letting him cry and listening to his many stories about his wife. I was in awe of his compassionate, empathetic, and humanistic approach, especially when he began to prepare this man for the fact that his wife might not live through the night. He handled the situation with such compassion — with such professionalism, in the truest sense of the word — that I learned volumes. Likewise, there is an attending here at Mount Sinai of whom we students speak in awe, because of his compassion, knowledge, and respect. Not only is his manner exemplary, but we are all impressed with his choice to dedicate his life and career to serving the underserved in medicine through home visits and in other ways. On the other hand, as a student I have witnessed actions that, because they were in clear opposition to the qualities that we have been discussing, were equally important in my learning to define professionalism for myself. Thus, while I was formally taught in the classroom the framework within which to consider and understand the concept of professionalism, it was largely through observation, mentoring, and role modeling that the concepts were finally solidified and internalized.

The final question that I will address is what, in my opinion, Mount Sinai can do better to promote professionalism in its students. First and foremost, teach us more of the historical context of professionalism in America (1, 2). Teach us about the noble tradition of doctors here and their long history of obligation to society, so that we can truly understand where medicine has been and where it is going (1, 2, 5, 6). Teach us that, in fact, the autonomy which the field of medicine has enjoyed historically was granted in exchange for a stated commitment to altruism and public service (1, 2, 5, 6). But also teach us about lapses in professionalism that occurred in the past so that we can learn to recognize them and to prevent them effectively (1, 5). Likewise, acknowledge the inherent conflict between professionalism and a doctor's own financial security and how these issues have been dealt with in the past and how they will be addressed in the future (2). Most important, teach us about how professionalism as we know it is threatened by forces such as managed care and how the field of medicine must adapt (2, 5). How can we be humanistic and compassionate when we have only 10 minutes to see the patient? How can we truly care for our patients if insurance companies are telling us which tests to run, which medicines to prescribe, and how much time we will be allocated to do it? Give us the knowledge and the tools so that we can maintain the principles of professionalism as health care reform continues — so that we, the next generation of doctors, can lead the reform ourselves.

As a final note, I think that it is crucial to mention that many medical students — not all, but probably most — come to medicine with some sense of a higher calling. Most, including me, initially are idealistic, altruistic, and humanistic. I remember a lecturer who once implored the students in our first-year class to write down on a small scrap of paper those qualities we aspired to as physicians. He urged us to carry this paper close to us, in our book bags or in our wallets, so that we could pull it out and remind ourselves why we were here at times when it might be less obvious to us — when we found ourselves in the midst of chaos or stress. I have often felt during my medical education, beginning with the anatomy lab and continuing through the various clerkships, that my personal challenge was to maintain this humanism and idealism throughout the years of medical school, to resist the desensitization and disillusionment that were probably natural. I know that many of my classmates felt the same way. And many of them feel as if they have lost too much through the process. It is ironic that the system itself squelches so much of the idealism and the spark of professionalism that educators are, in the classroom at least, trying to teach, preserve, and foster. As important as formally teaching professionalism and providing role models whom we can emulate is the need to reform the system (4, 5). By "the system" I am referring both to the system of managed care that threatens professionalism, at least as it once existed, and the system of medical education that, at times, causes students to lose sight of the amazing privilege that we are being granted: that is, to be part of what I believe is the most meaningful and gratifying calling that there is.

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Summary Remarks:

The Implications of Professionalism for Medical Education

Arthur Rubenstein, M.B.B.Ch.

Abstract

Can professionalism be taught and measured? In the medical school environment, particularly with clinical encounters occurring in the first year, a focus on professionalism should begin right away. Attitudes and behavior of the students are strongly influenced during these encounters between physician-mentors, and patients and their families at the bedside or in the clinic. Careful listening and the demonstration of communication skills during these encounters are paramount. Asking questions may be better than telling students what to do. The faculty must provide thoughtful and constructive critiques and must have a mechanism for follow-up. By paying attention to how students really function, we might better teach the precepts of professionalism without adversely affecting their own well-being.

Key Words: Professionalism, medical education, medical school curriculum.

CAN WE MEASURE PROFESSIONALISM among students? This has been a vexing question because it is one thing to teach professionalism, and another to evaluate it. I want to draw your attention to the article in *Academic Medicine*, by Maxine Papadakis and her colleagues (1) at the University of California, San Francisco (UCSF). She points out that one can start evaluating professionalism, particularly now that we have clinical encounters in the first year, right from the beginning of medical school. And perhaps there are ways to influence professionalism during the socialization process of medical training. Again, I agree that teaching professionalism has to be done around patients. The place has to be at the bedside and the encounter has to be between the physician, the patient and the family. Maxine has developed a framework for doing that. The mentor completes an evaluation sheet at every clinical encounter. The curriculum can be structured in terms of this evaluation: reliability and responsibility, rapport with and respect for patients and families, relations with preceptor and office staff, motivation and maturity, flexibility, initiative and self-directed learning. The idea is that the students know that they are being evaluated along these lines, and the instructors, their mentors, tell them that these are issues that will be looked at.

Certainly professionalism or ethics cannot be taught by sitting at home in front of a computer. There has to be some obligatory participation. Preparation and self-directed learning are of course important. Communication skills are also important: listening carefully, contributing constructively, giving and receiving feedback, and respectfully engaging with a person, particularly with someone who has opinions different from those of the student. It has to be made clear to students when they begin medical school that a negative rating on these parameters, irrespective of their cognitive skills and knowledge success, may prevent them from graduating.

In academic medical centers, it is the whole atmosphere that creates the balance in terms of how students, residents, and fellows emerge. The sum total of all the mentors and role models convey the importance of professionalism. Deans, chairmen, division directors all have an

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enormous responsibility and a huge role in terms of creating this climate. There's no doubt in my mind that this collection of role models and mentors has an enormous impact on medical students.

Just as it was during the apprenticeship system, many former students speak or write to you or your colleagues and say they remember x, y, z. Of course they don't tell you the bad things they remember. Somebody else tells you that. But many former students tell you that thirty years ago they were on rounds with you and they remember when you did this and how it never left them. Of course I remember such experiences during my medical school training in South Africa among my own mentors. I can remember many ward rounds, including interactions with patients, and the attitude and behaviors which particular mentors imparted to me. We can't minimize that. To me, this activity must play a dominant role in any medical center that seeks to promote the professionalism of its graduates.

I came across an article, outside of medicine, about role models. I don't know how many of you have read this book, which has just been written by Barbara Sand (2). It's about Dorothy Delay, who apparently is one of the great musician teachers of all time. Very few people know about her because she never did anything except teach great people like Itzak Perlman, Sarah Chang, Madori, Kennedy, Chen, Duffy and so on. And only recently has the impact of this wonderful woman become known. Ms. Sand tried to analyze why this woman has had such a huge impact on a number of genius musicians. I found it fascinating. Something to titillate your fancy. Here are some of the things that we can learn from this wonderful mentor.

- Teach the student, not the subject. Of course this personal involvement with young people usually leaves an indelible impression.
- Have high expectations. Many of us tend to accept mediocrity. That's clearly not acceptable.
- Be positive. Many of us are always critical in a negative way rather than the opposite. It takes thoughtfulness to be constructive.

Many people here have talked about how you actually create an environment for professionalism, not by telling students what to do, but by asking questions. Coming originally from the University of Chicago, watching the Socratic method being used at its best, I can tell you that using it with medical students is enormously powerful. They come expecting to be told facts or to find them in syllabi or Internet curricula. When you really challenge them, as many of us have done, they respond. I learn from them.

One of the things Delay stressed is to "be yourself." You can't change. If you are yourself all of the time, students trust you and clearly that's important. "Try to analyze the problems they have." When we make the situation too complex they can't respond to it. We can't talk about finances, and managed care, and time commitments in academic medical centers. We have to be able to dissect the issues and discuss them step by step, so that they can build on basic concepts and benefit from the discussion. "Feedback, showing people how they have evolved, and rewarding them" for their progress is very important. We tend not to do that in a systematic way. I'd like to think about how we might do that better. Delay used all kinds of tricks to do this. One involved a young student who couldn't play the violin fast enough to keep up with the metronome. Delay stopped the metronome and she got him to play slowly. Then she said "a little faster, a little faster, a little faster." When she finally put on the metronome, he was going faster than it was. That's trickery in the best sense of the word. Another thing is, "you can't teach everything." We have to choose certain things to teach and get students to learn the rest themselves. That's true adult education. Being a team player is critically important in medicine. I guess if you are part of an orchestra, you can't play by yourself. Another point she made is "attend to everything." We don't do that very well. We don't think about the student's family or about how they are going to function in the system. Maybe if we paid more attention to how students really could function in a system, and being professional without harming their own well-being, we would teach them that they could do both of these with some modest but not overwhelming compromises. And then the point that I think is so important with young people is "to follow up." One of the most rewarding parts of medical education is to watch their careers blossom and to keep in touch with them. Now that e-mail is available, I e-mail a couple of students every few months. When I get replies from them, it's like I've given them a pot of gold.

It's quite clear that techniques and opportunities exist today for teaching professionalism. I'm an optimist about the profession. Despite some real problems, I think we can do a whole lot better, particularly by attending to the culture of academic centers, by seeing that leadership is much more pro-active in terms of mentorship, and maybe even by measuring it along the lines suggested by Dr. Papadakis.

Mentoring is clearly the most effective means of transmitting values. It is an educational exercise. There must be agreement on the objectives. In fact, when you talk about professionalism, the faculty has to agree about what it believes constitutes professionalism. The UCSF's program is obviously very, very effective but it's only addressing about forty or fifty percent of what constitutes professionalism in modern society. Mentoring requires that those agreed-upon definitions and sets of attributes be taught by the entire faculty. The first thing you have to do is to start with a faculty development program that has its origins in an agreed-upon definition of professionalism and then follow with a very extensive development program on how you're going to transmit those values.

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Panel Discussion

Issues in Medical Ethics

Rosamond Rhodes, Ph.D., and Daniel A. Moros, M.D.

Question:
After six years of medical training I am about to become a professional, and I realize that I have no understanding of the business end of medicine. I wonder if you can address the professionalism of the business of medicine. No one has trained me to deal with patients who are underserved — should I charge them or not charge them, and so forth? Should our training include something about this?

Dr. Mark Siegler:
Historically, medical students, residents and fellows have been protected from this kind of knowledge. Even clinical faculty was protected from a lot of the business aspects of medicine, so we were not well prepared to teach this. I think that it would be dishonest these days if we don't educate our trainees about the world that they are about to enter. I certainly do not think it should dominate medical education, but I think it is crucial that graduates of our programs understand the world that they are going to be entering, so that they can be best prepared for it.

Dr. Samuel Bloom:
As a longtime medical educator and observer of the medical profession, I think that medical schools and medical educators generally have made the decision that it is essential for the training period to concentrate on the science and clinical practice of medicine. And that only by an immersion in modern medicine can you produce a doctor. I disagree with this intellectually, but I have great respect for the fact that the medical profession has chosen this method. There should be preparation for the world of medical practice as well as the world of medical science and clinical decisions and judgment. But I seem to be a minority voice among medical educators and am often told that I don't understand because I am not a physician. It is not very sensible to turn anyone loose without preparation for the realities in which they are going to work.

Audience:
What behaviors get medical students and residents called to the dean's office the quickest? Are they breeches of professionalism or something else?

Dr. Fred Hafferty:
What gets you in the most trouble is disrespecting, questioning a higher authority, failing to do something that you should have done, and general laziness. I don't think that it is failure in ethical and moral issues that gets you into trouble.

Jennifer Fehser:
I'd add cheating and dishonesty to that. I am a fourth-year medical student and from what I have seen, that is what gets people into the most trouble.

Dr. Roger Cornwall:
What gets you in trouble and into the chairman's office the fastest on my service is failure to answer a page — that is considered a breech of professionalism. Unfortunately, the residents who get called in for that don't see it as a breech of professional conduct but rather as disobedience to the hierarchy.

Dr. Rhodes:
What about the virtue of responsiveness and the importance of presence, showing up, calling, and spending time talking to patients?

Dr. Edmund Pellegrino:
I wonder if we wouldn't advance a little further in this conversation if we dropped the term "professionalism." What you are talking about is a moral obligation — to respond to a call is a moral obligation. When you are called on the carpet for a failure of ethical obligations, that relates to professionalism, but that is secondary.

Ethics is at the heart of the matter. I think that too much concentration on "professionalism" gets us off the major factor, which is that we have major obligations which go with being a physician because of the nature of what we do! I don't think there is any way of getting off that hook. You can try to get off it by saying that because the chief wants this, it is a hierarchy issue. No, it is your duty as a physician!

Dr. Cornwall:
I think this point is sadly lost on our residents. For the most part, residents think that they have a professional duty to their superiors to follow the rules. They miss the whole point that those rules are to help us face our moral responsibilities.

Dr. David Neirman:
That's exactly right. Ethics is the job of the director of the residency program or the director of the service. One of my problems is that today the directors of clinical services really don't run the service. Often they are not present and they are not commenting on the ethical issues.

Audience:
How do we get medicine, as a profession, as a collective, back to making ethical and moral arguments against managed care requirements? How do we get the profession to address policies that are preventing us from practicing medicine properly, instead of arguing about pennies?

Dr. Stephen Latham:
You are right on that matter. As far as I'm concerned, our professional organizations have failed totally. They have become corporate entities. They have become unionized. They have become a guild. They have become loyal to each other rather than concerned with representing us as a moral community. I think the existing organizations today have lost their capacity to convince the public that they are acting in their interest. I don't know how to bring back the concern for the public interest, but I don't think we can do it with existing organizations.

Audience:
Dr. Pellegrino's talk persuaded me that professionalism is tied up with unions and with trade activities. It is a reality constructed by organizations. Instead of using the word "professionalism," we should talk about professional virtues. That phrase "virtue" gives a very clear signal.

Dr. Pellegrino:
I think the word "professionalism" is out there and a lot of people have rallied around it. It is not going to be so easy to get rid of it. We may need clarification of its fundamental basis.

Dr. Latham:
There are some areas where we have options and some areas where we don't. Professionalism is entrenched in our law, in our culture, in our society. It is part of the tradition of medicine. We can't get rid of the word. In the sociology literature, someone could write forty pages saying how bad the word is and that we shouldn't use it. But we really don't have any choice. We are stuck with the word "professionalism." Since we are stuck with it, we had better define it properly, teach it properly and convince the public that it has a positive, and not a negative, impact. I also want to say that many existing associations are doing their very best to promote a positive professionalism.

Audience:
Dr. Pellegrino expressed many deep concerns about the ability of the current organizational structure to lead significant reform of behavior. Another speaker raised the issue that the application of antitrust law and the development of Medicare in the United States may have caused the profession to significantly lose the ability to police itself and, in essence, to reform itself. I would like to hear what is happening in Europe in terms of the medical profession's ability to police and reform itself.

Dr. Thomas Rütten [panelist]:
In an authoritarian system, as medicine tends to be, I think that if reform is possible it has to come from those who practice the profession. We can't expect reform to come from the top. In Europe, people have been talking about reform of the health care system for decades without changing the everyday practice of physicians, aside from some financial changes for certain groups of practicing physicians.

What has been said about authority is crucial both for medical ethics and for professionalism. We cannot rely on authorities exclusively, even if these authorities are role models in the best sense of the word. As long as we do, we are at risk of picking the wrong ones. Those who follow the wrong role models can turn from moral physicians into criminals without understanding their transformation. We have to educate students, and ourselves, to be independent thinkers and to maintain a critical attitude toward whatever tests they confront, whatever structures, institutions, professional practices they encounter. Reason should be the prime authority for the physician's behavior.

Dr. Cornwall:
I would like to echo the comment that change probably cannot come from the top. I say that as somebody who is close to the bottom. We need to work on the inclusion of the young generations of doctors, including medical students and residents, in these discussions. A lot of attention needs to be paid to the opinions of these people.

Dr. Neirman:
Why wait to be included? Why not do something — I'm serious about that. You may not be invited to the party, but if you feel as you do and have a very fundamental understanding of the questions, you can challenge the older generations. Students can do something. Waiting to be invited is not the way to go about it.

Dr. Hafferty:
The request for reform from the bottom up is very sound, but it also makes me think of a paradox. We are living in a period of medical education reform that is dominated by the principle of activating the student, student-centered learning, problem-based learning. While there is a lot that can be done from the bottom up, it is very difficult to change the feeling of being at the bottom. Students and residents are at the bottom because of the social structure of medicine and the organization of the medical school. There is a hierarchy of status, and we retain the boundaries of the uppers and the lowers. So the paradox is that we encourage the people at the bottom to be active, to learn, to participate, to be part of the team. But at the same time, we remind them that they are still at the bottom and they are supposed to mind their p's and q's. We do this and we have no awareness of the duplicity of it. When students leave the medical school, they are going to encounter the same kinds of organizations — power driven and hierarchical — in which there are status boundaries. You have to smash your way from one level to the other. I do not believe that professionalism, in itself, can overcome these status and structural barriers.

The Cardiac Gap Junction:

A Potential Therapeutic Target in the Treatment of Heart Disease

Fangyu Liu, B.S., and David E. Gutstein, M.D.

Abstract

Cardiac gap junctions have been implicated in maintaining cardiac conduction and function. In cardiac disease, expression of connexin43, the most abundant ventricular gap junction protein, is markedly abnormal, a process termed "gap junction remodeling." To date, however, the gap junction has not been directly targeted therapeutically in cardiac disease states. Therefore, we have developed novel and complementary experimental models to investigate whether loss of connexin43 expression in the heart can be directly linked to the arrhythmic and functional complications of heart disease. In this article, we discuss how data from connexin43 conditional and chimeric knock-out mice support the hypothesis that gap junction remodeling is a key molecular feature underlying the high incidence of sudden arrhythmic death and exacerbating the ventricular dysfunction associated with acquired heart disease.

Key Words: Gap junction, connexin43, arrhythmia, heart.

A DETAILED UNDERSTANDING of biological function is vital to the process of developing therapeutic breakthroughs. In cardiovascular research, studies related to arrhythmia and heart failure may lead to therapies that will reduce the morbidity and mortality associated with these complications of heart disease. First, however, targets for these therapies must be identified. One such potential target is the cardiac gap junction. Gap junctions have been implicated in maintaining cardiac conduction and function (1–4). However, they have not yet been targeted in the treatment of cardiovascular disease. Therefore, using animal models, we have attempted to establish whether the gap junction could be an important therapeutic target in the diseased heart.

Gap junctions are arrays of intercellular channels that allow for the diffusion of ions and signaling molecules between cells. In the heart, gap junctions also form a low-resistance pathway for cell-to-cell conduction of electrical impulses. Gap junctions are made up of a family of proteins called connexins, of which more than a dozen have been cloned in mammals. While connexins are present in most tissues, the distribution of individual isotypes tends to be more restricted, with substantial overlap of different connexins in many tissues (5, 6). Certain tissues have one predominant connexin subtype, and single-gene mutations in these subtypes tend to have profound phenotypic sequellae. For example, in Schwann cells, which are responsible for forming the myelin sheath around nerves, connexin32 predominates. Mutations in connexin32 cause a demyelinating neuropathy in humans known as X-linked Charcot-Marie-Tooth disease (7). Similarly, connexin43 is the predominant subtype in the cardiac ventricles, and mutations of connexin43 have been implicated in cardiac developmental abnormalities (8).

In the adult heart, abnormalities of connexin43 expression have been described in a variety of cardiac disease states (9–11). Abnormal connexin43 expression in the diseased

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heart, referred to as "gap junction remodeling," consists of a loss of connexin43 expression from its usual location at the intercalated discs and a global down-regulation in the cardiomyocyte (12). Gap junction remodeling has been described in conditions such as myocardial infarction, hypertrophy, ischemia and hibernating myocardium, which are also associated with arrhythmias and ventricular dysfunction (9–11). In ischemic cardiomyopathies, gap junction remodeling is patchy, affecting areas of hibernating myocardium most profoundly (9). In the peri-infarct zone of experimental myocardial infarction in dogs, both altered electrophysiological properties and connexin43 dysregulation have been described (13, 14). The peri-infarct region, in addition, serves as an important focus for the generation of malignant ventricular arrhythmias, and is also the area involved in infarct expansion (15–17).

As a result of these data regarding gap junction remodeling, we hypothesized that dysregulation of connexin43 expression may be a key molecular feature of arrhythmogenicity and may contribute to ventricular dysfunction. In order to test this hypothesis, we had to develop novel models for the loss of connexin43. We were unable to use germline knock-out mice to study physiologic alterations in the adult heart, since these mice develop right ventricular outflow tract obstruction *in utero* and die perinatally from presumed pulmonary oligemia (18). The connexin43 germline knock-out phenotype was theorized to result from loss of connexin43 in the neural crest cell lineage rather than in the cardiomyocytes themselves (19–21). Thus, we elected to knock out connexin43 specifically in cardiomyocytes, using the Cre-loxP conditional knock-out system (22). For this system, loxP sites, 34 base pair palindromic sequences, are cloned into sites surrounding a gene of interest, which in our case was *connexin43*. The gene of interest is deleted upon exposure to Cre recombinase, an enzyme that catalyzes the recombination of the loxP sites. Cre recombinase can be introduced via a transgene, and its expression is driven in specific tissues by choosing a promoter for the Cre transgene that is active only in specific tissues. In order to generate the connexin43 heart-specific, conditional knock-out mice, we first created a line of mice in which we surrounded the *connexin43* gene with loxP sites (23). Next, we bred these mice with transgenic lines expressing Cre under heart-specific promoters (either alpha-myosin heavy-chain or myosin light-chain 2v in order to create two separate lines of conditional knock-out mice; see Fig. 1) (24, 25).

The connexin43 conditional knock-out mice had significantly lower levels of connexin43 in their hearts than did littermate controls, but did not differ from controls in gross morphology, histology, and echocardiographic dimensions and function. However, all the conditional knock-out mice died suddenly within the first few months of life, which contrasts with the normal murine lifespan of more than two years. To evaluate the cause of sudden death, we implanted miniaturized telemetry transmitters in a subset of conditional knock-out mice and monitored their heart rhythms continuously. All four monitored mice had ventricular tachycardia that degenerated into ventricular fibrillation at the time of death. In separate experiments, conduction velocity was found to be significantly decreased in isolated hearts from connexin43 conditional knock-out mice perfused with a voltage-sensitive dye (23). Thus, we found that heart-specific deletion of *connexin43* led to conduction slowing and sudden arrhythmic death.

Numerous studies (26) have predicted that cellular uncoupling may lead to the initiation of arrhythmias and their propagation. Cellular uncoupling may promote arrhythmogenesis by unmasking ectopic foci or by enhancing the generation of early afterdepolarizations (27). Cellular uncoupling may also lead to increased dispersion of action potential duration, which has been shown to promote reentry and arrhythmia propagation (28, 29). In addition, slow conduction as a result of cellular uncoupling can also provide the substrate for reentry (26). Potential mechanisms of arrhythmia generation and propagation are outlined in Fig. 2.

Interestingly, ventricular function was normal echocardiographically in the connexin43-conditional knock-out mice. However, since gap junction remodeling may be patchy in diseased myocardium (9), we wanted to model a more heterogeneous loss of connexin43. Therefore, we generated chimeric mice from connexin43 knock-out embryonic stem cells, using wildtype recipient blastocysts (see Fig. 3). The chimeric connexin43 knock-out hearts appeared grossly and histologically normal, but immunofluorescent staining showed a patchy loss of connexin43 staining throughout the myocardium. Conduction patterns in isolated chimeric connexin43 knock-out hearts perfused with a voltage-sensitive dye showed distinct areas of conduction delay resulting in scalloped and irregular epicardial conduction wavefronts. These conduction patterns differed markedly from the smooth wildtype con-

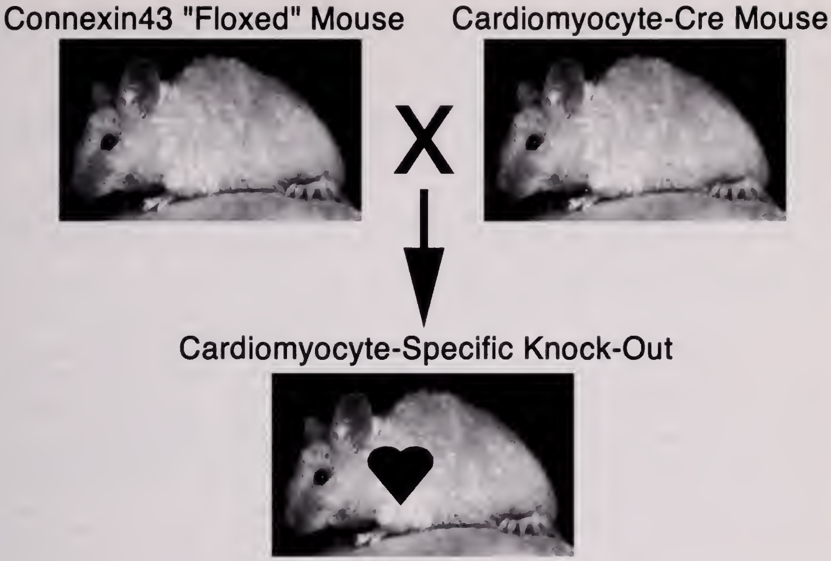
Connexin43 "Floxed" Mouse
X
Cardiomyocyte-Cre Mouse
Cardiomyocyte-Specific Knock-Out

Fig. 1. Schematic illustration of breeding strategy for the generation of cardiomyocyte-specific connexin43 conditional knock-out mice. Genetically altered mice with loxP sites flanking their connexin43 loci (connexin43 "floxed") were bred with transgenic mice expressing Cre recombinase under the control of heart-specific promoters in order to produce connexin43 conditional knock-out mice.

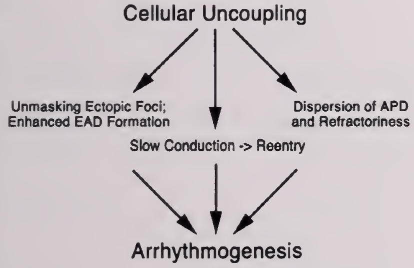
Cellular Uncoupling
Unmasking Ectopic Foci; Enhanced EAD Formation
Slow Conduction -> Reentry
Dispersion of APD and Refractoriness
Arrhythmogenesis

Fig. 2. Potential mechanisms of arrhythmia generation and propagation in the connexin43 conditional knock-out mouse. EAD = early afterdepolarization; APD = action potential duration.

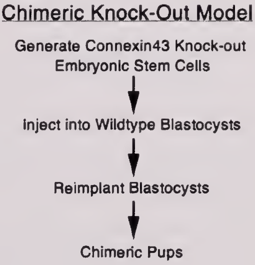
Chimeric Knock-Out Model
Generate Connexin43 Knock-out Embryonic Stem Cells
Inject into Wildtype Blastocysts
Reimplant Blastocysts
Chimeric Pups

Fig. 3. Strategy for the generation of chimeric connexin43 knock-out mice. Mouse embryonic stem cells with the connexin43 gene loci deleted on both alleles were injected into wildtype blastocysts and implanted into pseudopregnant females. The resulting chimeric embryos developed into chimeric mice that were used for the experiments described in the text.

trol patterns. In addition, ventricular systolic function in the chimeric mice was significantly depressed in comparison to controls (30). These findings suggest that loss of the normal pattern of electrical activation in the heart may result in disordered contraction and mechanical dysfunction.

The conditional and chimeric connexin43 knock-out models have provided important clues regarding the potential role of gap junction remodeling in the diseased heart. For example, heart-specific deletion of connexin43 does not perturb cardiac development, morphology or function. Loss of connexin43 in the heart, however, does lead to conduction delay and sudden arrhythmic death. On the other hand, patchy loss of connexin43 in the chimeric mouse is associated with discrete conduction defects and ventricular systolic dysfunction. Thus, our studies support the hypothesis that gap junction remodeling is a key molecular feature underlying the high incidence of sudden arrhythmic death, and exacerbating the ventricular dysfunction associated with acquired heart disease. Gap junctions may represent a worthwhile therapeutic target in patients at risk for lethal ventricular arrhythmias.

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